Endocrine Disrupting Chemicals and Women's Health Symposium

A Virtual Symposium

July 18–19, 2023

9am–4pm ET

OASH | Office on Women's Health

Welcome

Dorothy Fink, M.D.
Deputy Assistant Secretary for Women's Health
Director, Office on Women's Health
Department of Health and Human Services

Introduction To EDCs and Their Impacts On Women

Andrea Gore, Ph.D.

Moderated by Keiva Nelson

Introduction To EDCs and Their Impacts On Women

Andrea Gore, Ph.D.

Professor and Vacek Chair in Pharmacology

University of Texas at Austin

Introduction to EDCs and Their Impacts on Women

Andrea C. Gore, Ph.D.

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The University of Texas at Austin

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Of the hundreds of thousands of manufactured chemicals, about 1000 have been shown to be endocrine-disrupting chemicals (EDCs)

Endocrinology 153: 4097 (2012)

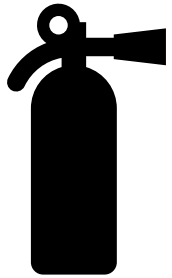
POSITION STATEMENT

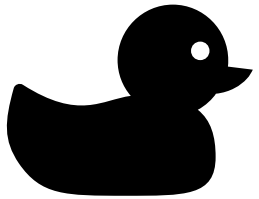
Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

"An exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action"

Categories of EDCs

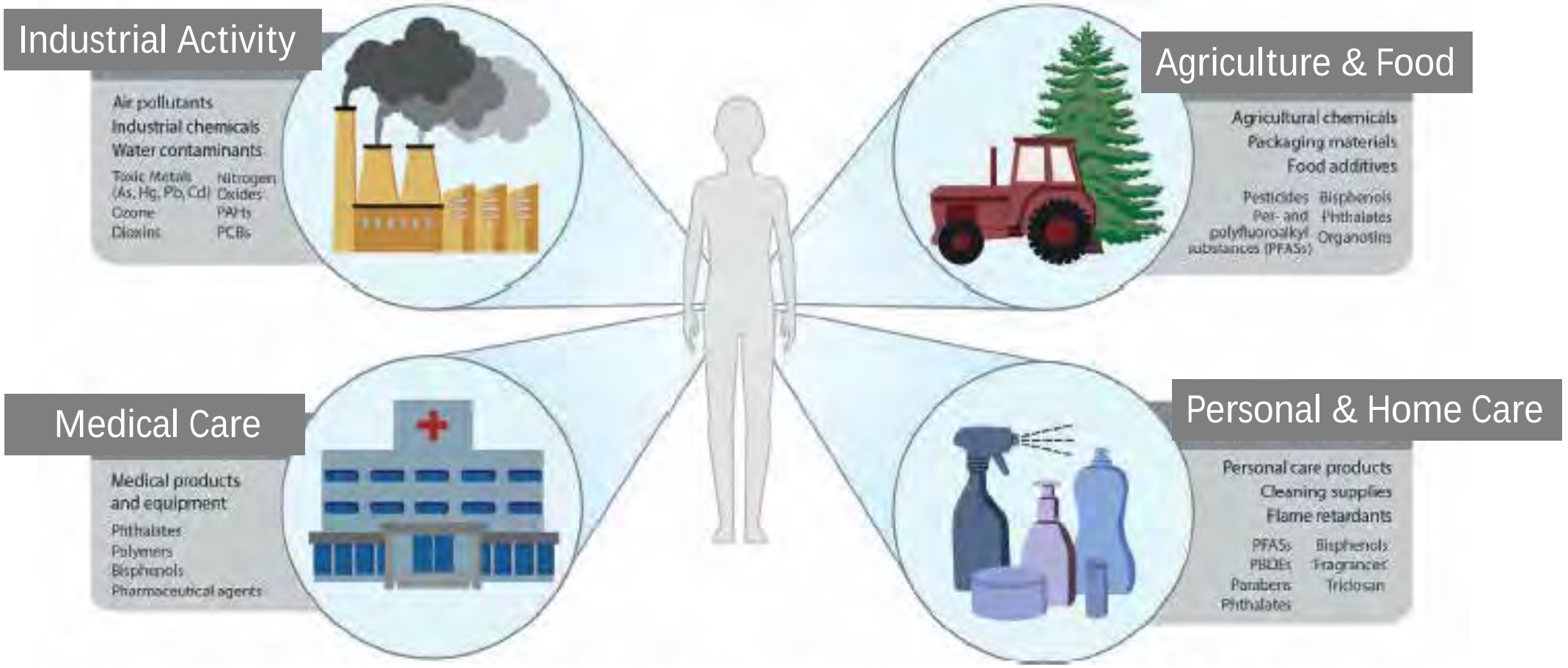




Category/Use	Example EDCs
Pesticides	DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate
Children's products	Lead, phthalates, cadmium
Food contact materials	BPA, phthalates, phenol
Electronics and Building materials	Brominated flame retardants, PCBs
Personal care products, medical tubing	Phthalates
Antibacterials	Triclosan
Textiles, clothing	Perfluorochemicals

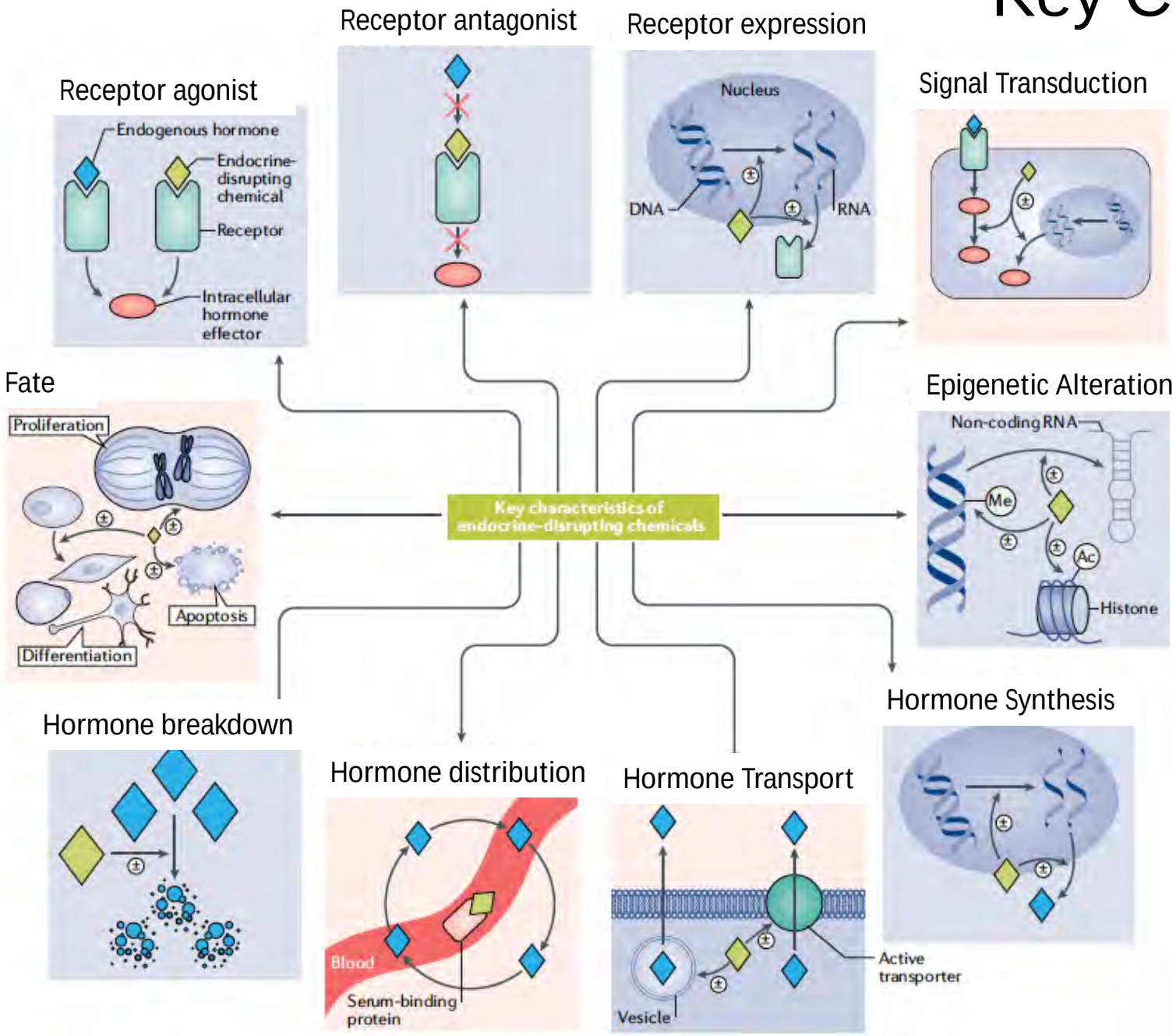
Gore et al. 2014, Introduction to EDCs (IPEN)

Human exposures to EDCs



Schulz & Sargis (2021) Advances in Pharmacology 92: 419.

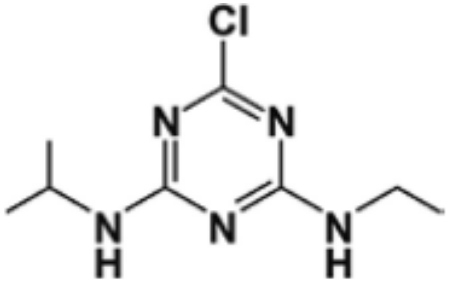
Key Characteristics of EDCs



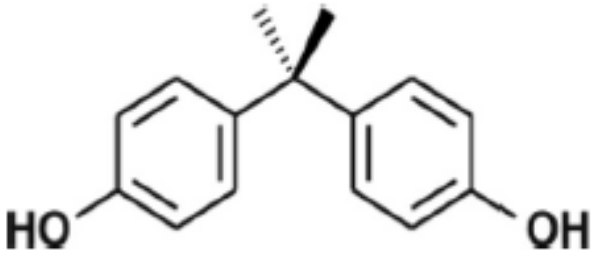
La Merrill et al. 2020, Nat. Rev. Endocrinol. 16: 45

EDC Examples & Structures

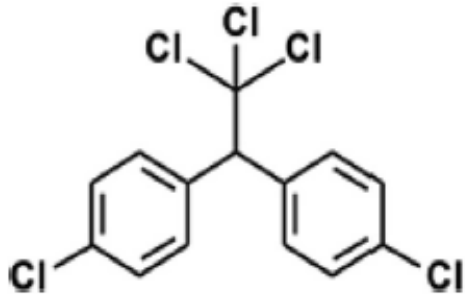
Atrazine (herbicide)



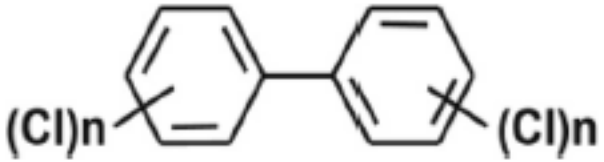
Bisphenol A (plastics)



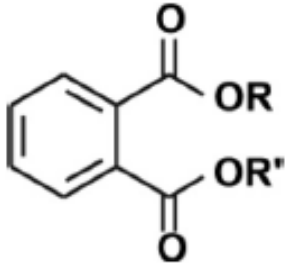
DDT (pesticide)

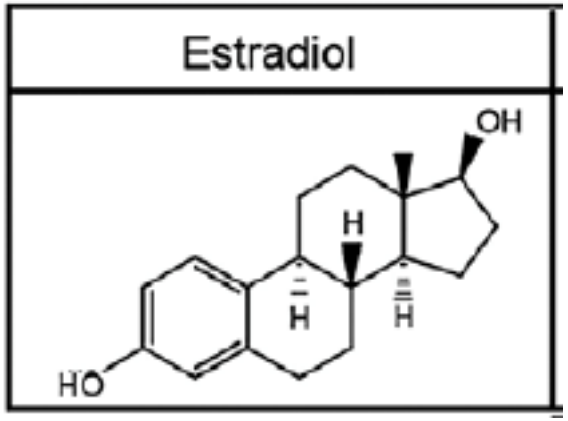


PCBs (industry)

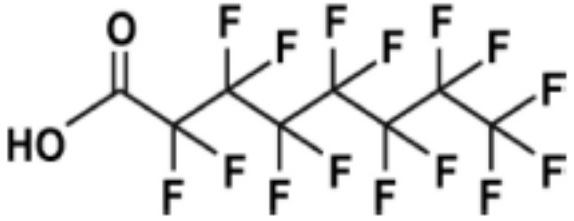


Phthalates (plastics, cosmetics)

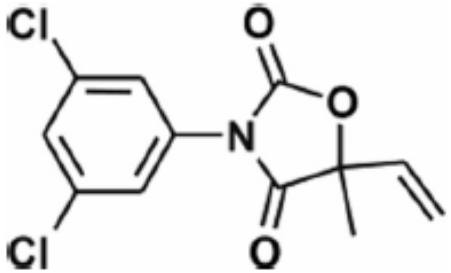




PFOA (surfactant)



Vinclozolin (fungicide)



Evidence that EDCs Affect Human Health

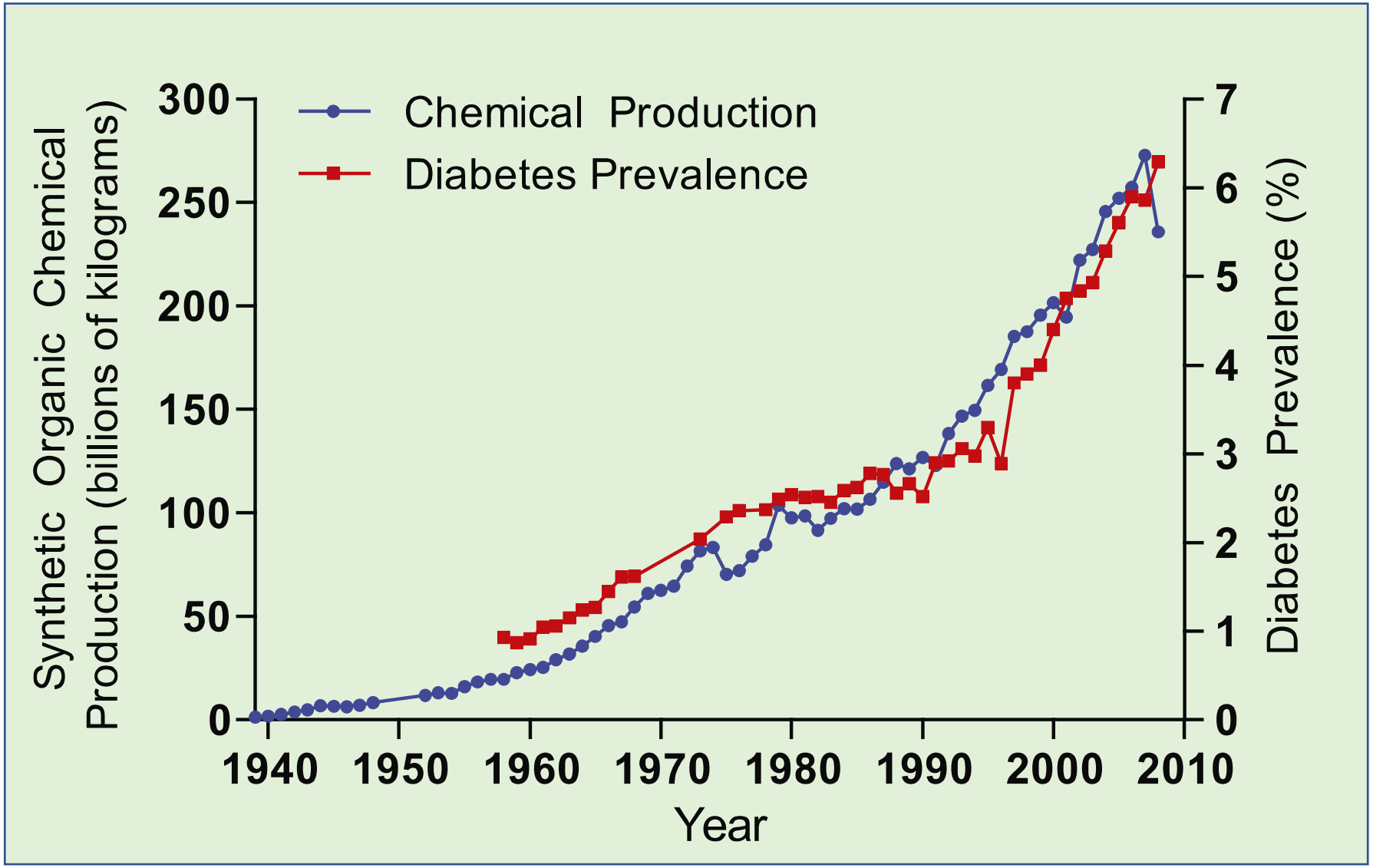
Disasters and Industrial Accidents:

- Seveso, Italy – dioxins
- Japan, Taiwan – industrial chemicals (PCBs)

Epidemiology:

- Agent Orange exposure and prostate cancer
- Twin studies showing that environmental factors play the principle role in hormone-sensitive cancers
- Correlations between increased chemical synthesis and chronic diseases

Correlations between chemical production and diabetes



Neel & Sargis, Diabetes 60: 1838 (2011)

EDCs and Human Health

Biomonitoring:

- NHANES database (US CDC) shows EDCs detectable in human fluids (urine, blood, breast milk, umbilical cord blood)
- Individual studies overwhelmingly detect chemicals in all humans

EDCs and Human Health

It is not possible to prove cause and effect in humans in the case of EDC exposures and chronic, complex diseases.

This is where experimental animal studies have been invaluable and irreplaceable.

The convergence of human observational and epidemiological data, together with lab animal studies, have led to the strong conclusion that EDCs are environmental factors increasing risk of endocrine and neurological disorders.

Moving EDCs into the Mainstream: Endocrine Society Scientific Statements (2009, 2015)

Endocrine-Disrupting Chemicals

An Endocrine Society Scientific Statement

Evanthia Diamanti-Kandarakis, Jean-Pierre Bourguignon, Linda C. Giudice, Russ Hauser, Gail S. Prins, Ana M. Soto, R. Thomas Zoeller, and Andrea C. Gore

2009

EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

2015

THE ENDOCRINE SOCIETY®

Endocrine Society Scientific Statements (2009, 2015)

- Obesity, diabetes, and cardiovascular disease
- Female reproductive health
- Male reproductive health
- Hormone sensitive cancers in females
- Prostate gland
- Thyroid gland
- Neurodevelopment and neuroendocrine systems

Endocrine Society Scientific Statements (2009, 2015)

- Obesity, diabetes, and cardiovascular disease
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Female Reproductive Health

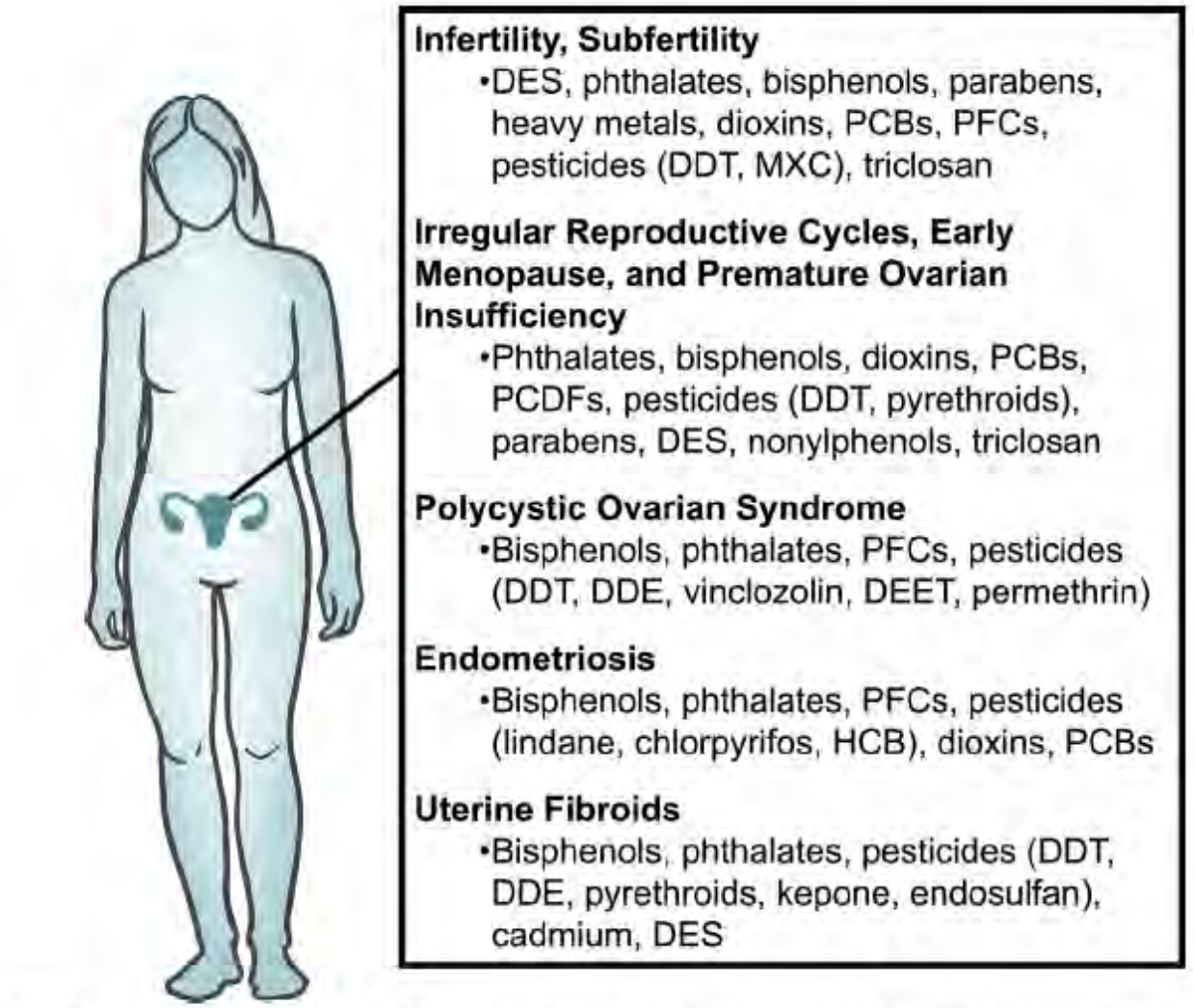


Fig. 1 A summary of EDCs associated with female reproductive disorders.

Laws…Flaws (2021) Advances in Pharmacology 92: 151.

EDCs: Special Considerations for Women

- EDCs have a disparate impact dependent on race and ethnicity, socioeconomic status, and other factors.
- Women have more body fat than men and can accumulate lipophilic substances such as EDCs.
- Women tend to use more personal care products (e.g. cosmetics, hair products).
- Women have unique physiological demands during pregnancy.
- Environmental exposure of a pregnant women can potentially affect the developing fetus.

Ø Effects of EDCs can differ profoundly between females and males.

Personal Care Product Exposure Tied to Girls' Early Puberty

— Associations weren't seen among boys using parabens, phthalates

by Kristen Monaco, Staff Writer, MedPage Today December 28, 2019

THESE CHEMICALS DISRUPT THE SEXUAL DEVELOPMENT OF CHILDREN — AND THEY'RE EVERYWHERE

Chemicals in cosmetics, soaps tied to early puberty in girls

By Lisa Rapaport, Reuters Health

5 MIN READ

Use Patterns of Leave-on Personal Care Products among Swiss-German Children, Adolescents, and Adults

Eva Manová [1], Natalie von Goetz [1,*], Carmen Keller [2], Michael Siegrist [2] and Konrad Hungerbühler [1]

Int J Environ Res & Publ Health 2013

Maternal Concentrations of Polyfluoroalkyl Compounds during Pregnancy and Fetal and Postnatal Growth in British Girls

Mildred Maisonet,[1,2] Metrecia L. Terrell,[1] Michael A. McGeehin,[2] Krista Yorita Christensen,[1] Adrianne Holmes,[2] Antonia M. Calafat,[2] and Michele Marcus[1,2,3]

The Exposure of Fetuses and Children to Endocrine Disrupting Chemicals: A European Society for Paediatric Endocrinology (ESPE) and Pediatric Endocrine Society (PES) Call to Action Statement

Niels E. Skakkebaek, Jorma Toppari, Olle Söder, Catherine M. Gordon, Sara Divall, and Martin Draznin

JCEM 2011

Environmental Exposures During Pregnancy and the Developing Fetus

DOHaD: Developmental Origins of Health and Disease

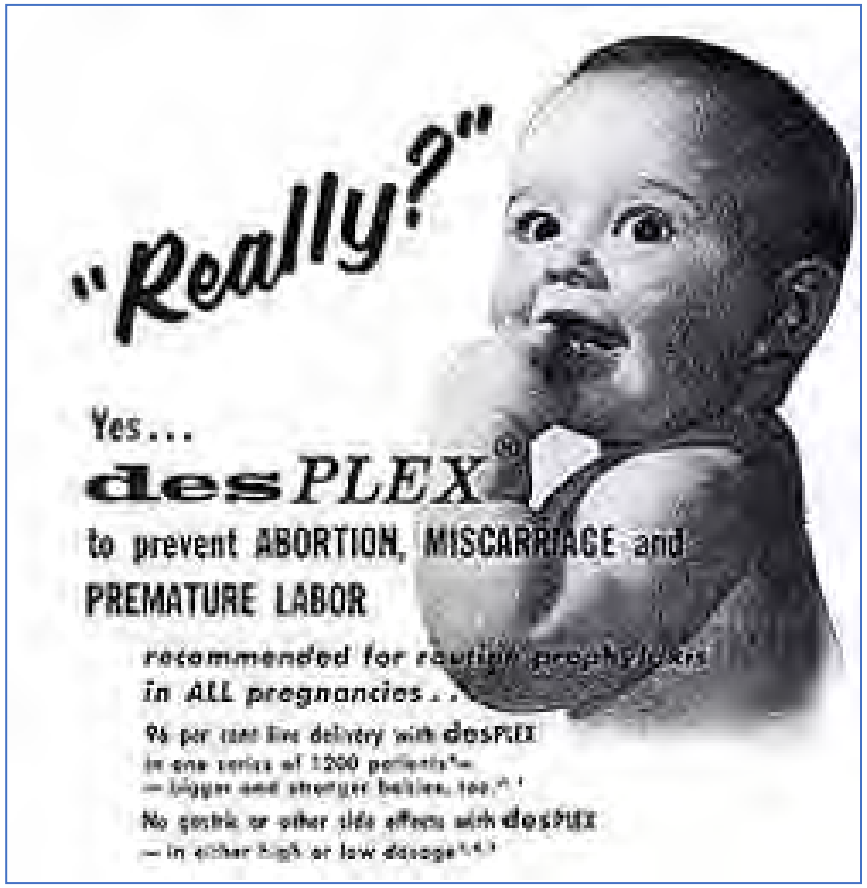
- The timing of exposure to EDCs is everything – fetus, infant, child, puberty
- The manifestation of disease may not occur for years or decades

Critical periods

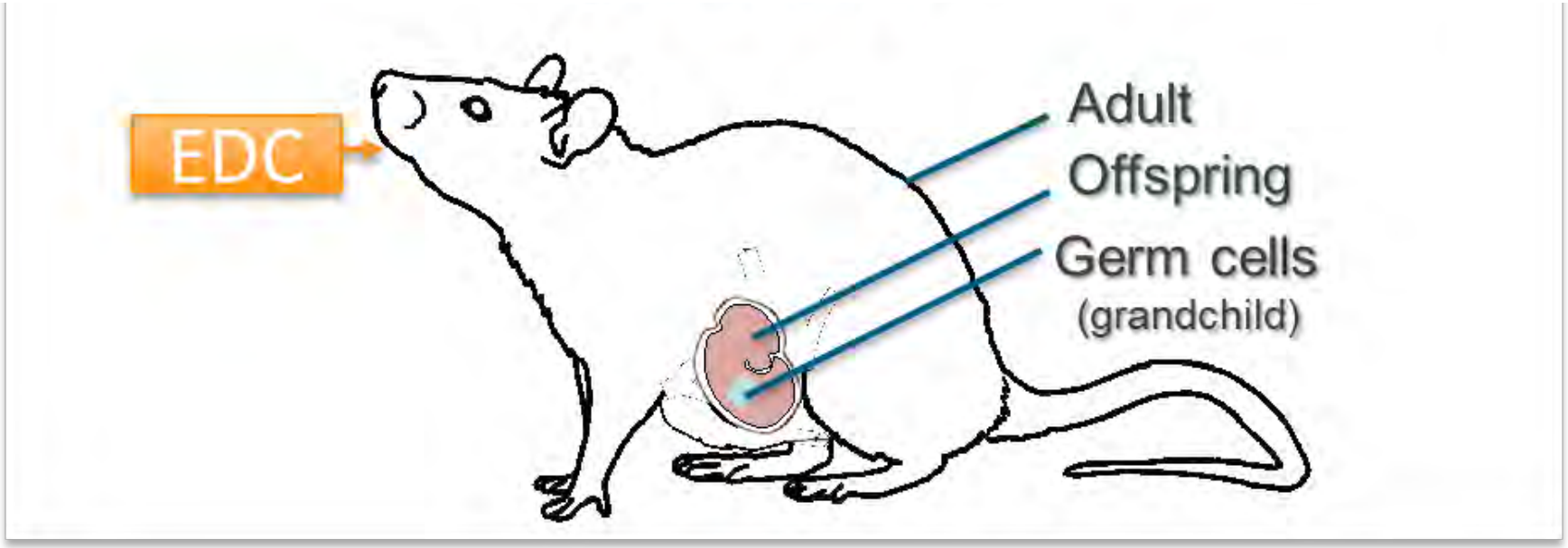
- Particular vulnerability during life stages when there is rapid developmental change and hormone sensitivity.

DES (Diethylstilbestrol) as the poster child for DOHaD in humans

- Pharmaceutical estrogens can cross the placenta
- The fetus is sensitive to these substances
- Developmental ‘programming’ happens in a sex- and timing-specific manner

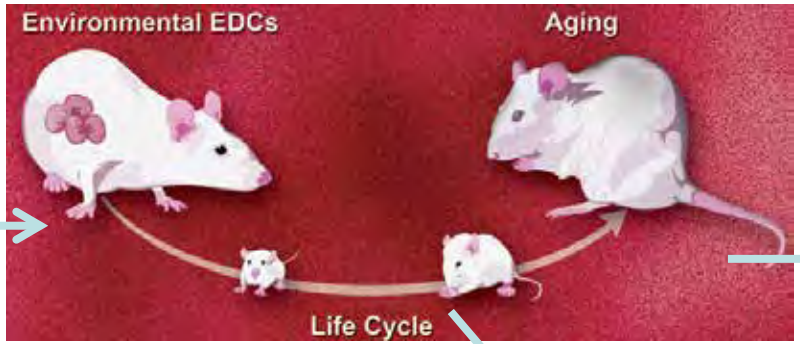


The Rodent DOHaD Model: Proving cause and effect



Modeling EDC effects using real-world scenarios

Developmental exposure *in utero*



Future Generations

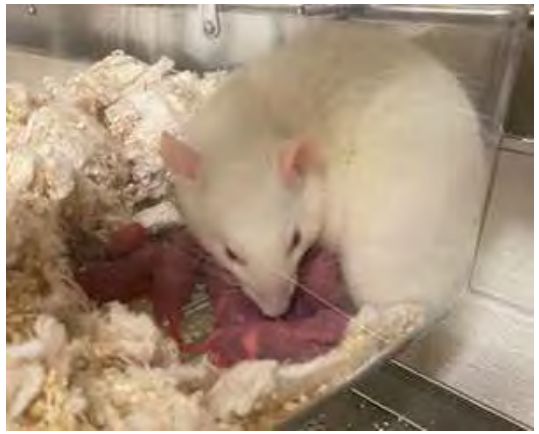
- Legacy vs. contemporary EDCs
- Combination of direct and heritable effects
- Lineages (maternal, paternal)
- Sex differences
- Epigenetic programming mechanisms

Direct Developmental Exposure (DOHaD)

- Multiple chemicals across the lifespan
- EDCs in combination with other life stressors
- Sex differences

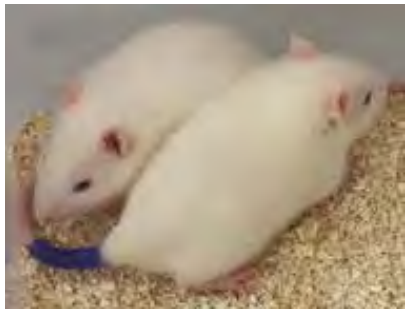
Overview of EDC effects in our DOHaD model

Neonates



- Body weight
- Anogenital distance
- Hypothalamic gene expression
- Hypothalamic protein expression
- Sex differences

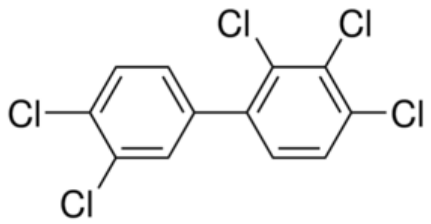
Adolescents



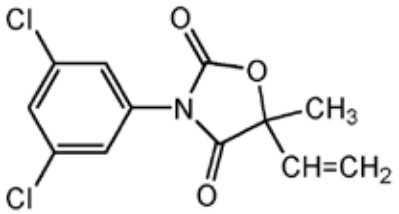
- Body weight
- Timing of puberty
- Hypothalamic gene expression
- Hypothalamic protein expression
- Social behaviors
- Sex differences

Adults & Aging

- Body weight
- Hypothalamic gene expression
- Hypothalamic protein expression
- Social behaviors
- Sexual behaviors
- Mate choice
- Reproductive aging
- Epigenetic marks (DNA methylation, microRNAs)
- Sex differences



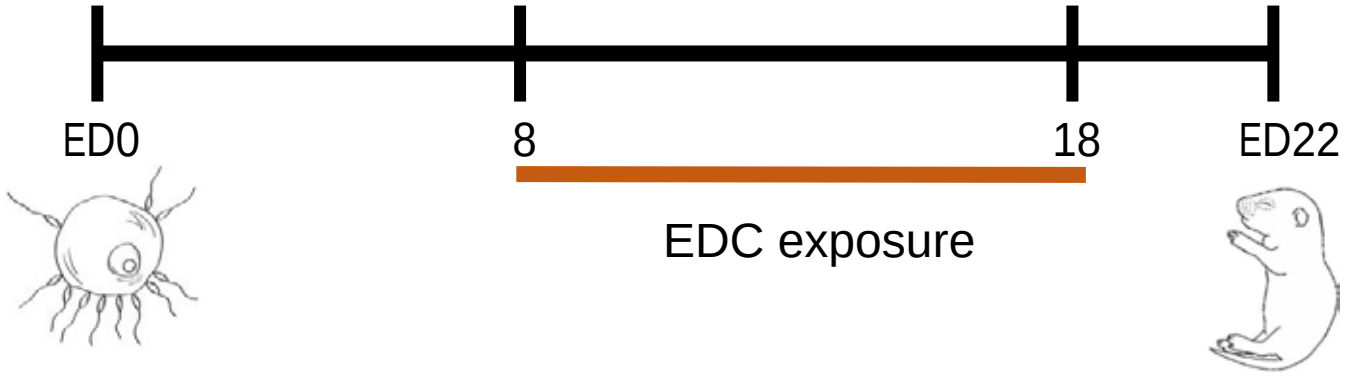
Aroclor 1221



Vinclozolin

-polychlorinated biphenyl (PCB)
-weakly estrogenic
-used as industrial lubricant
-dielectric fluid in transformers, capacitors
-banned 1979
-contaminated soil/water

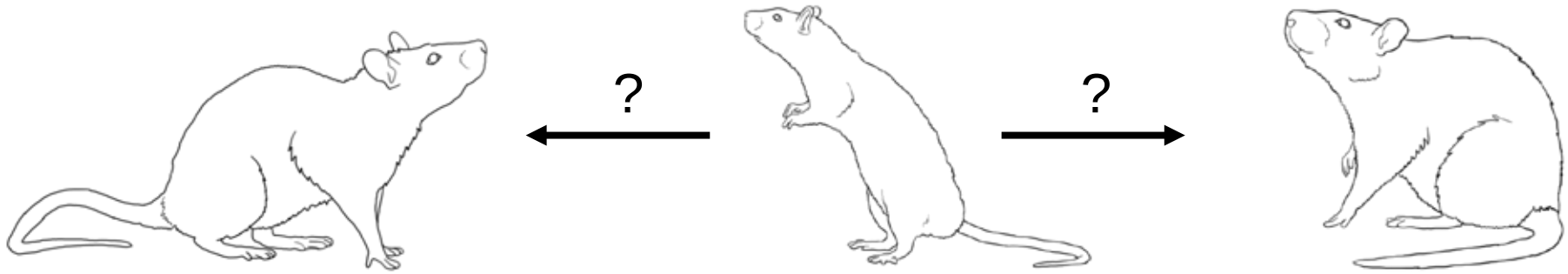
-dicarboximide fungicide
-anti-androgenic
-used on vineyards, sod, fruits and vegetables
-banned EU, AUS (but not U.S.)
-contaminated food/drink



Prenatal EDCs: Effects on mate preference

A fundamental question is whether EDCs impair reproductive success.

Female rat prenatally exposed to EDC or vehicle

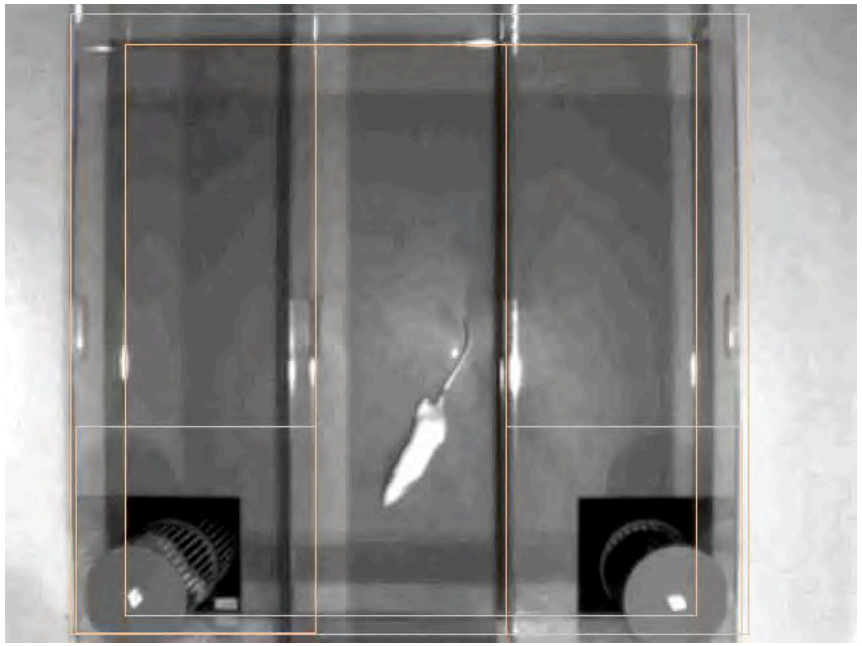


Male rat (no T)

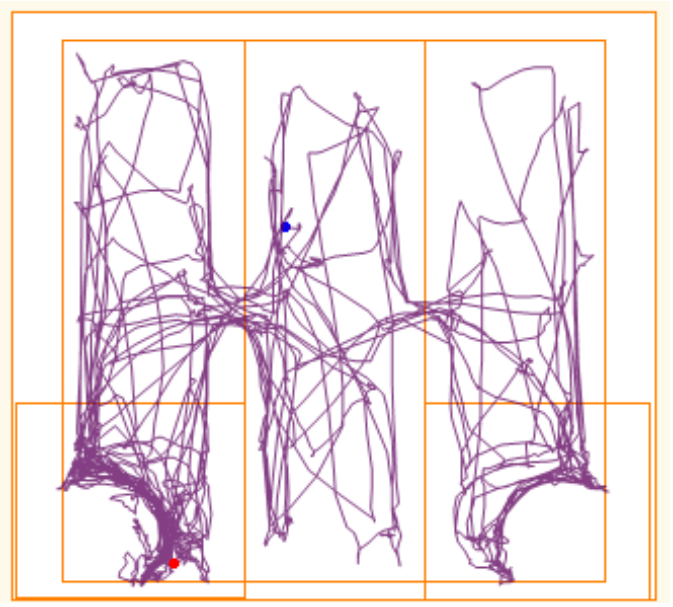
Male rat (with T)

Mate preference test

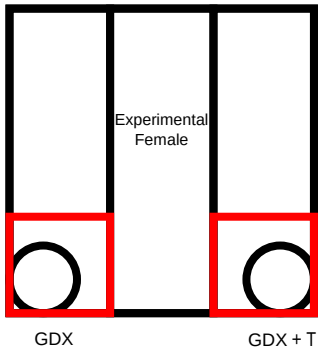
Male 1
(T)

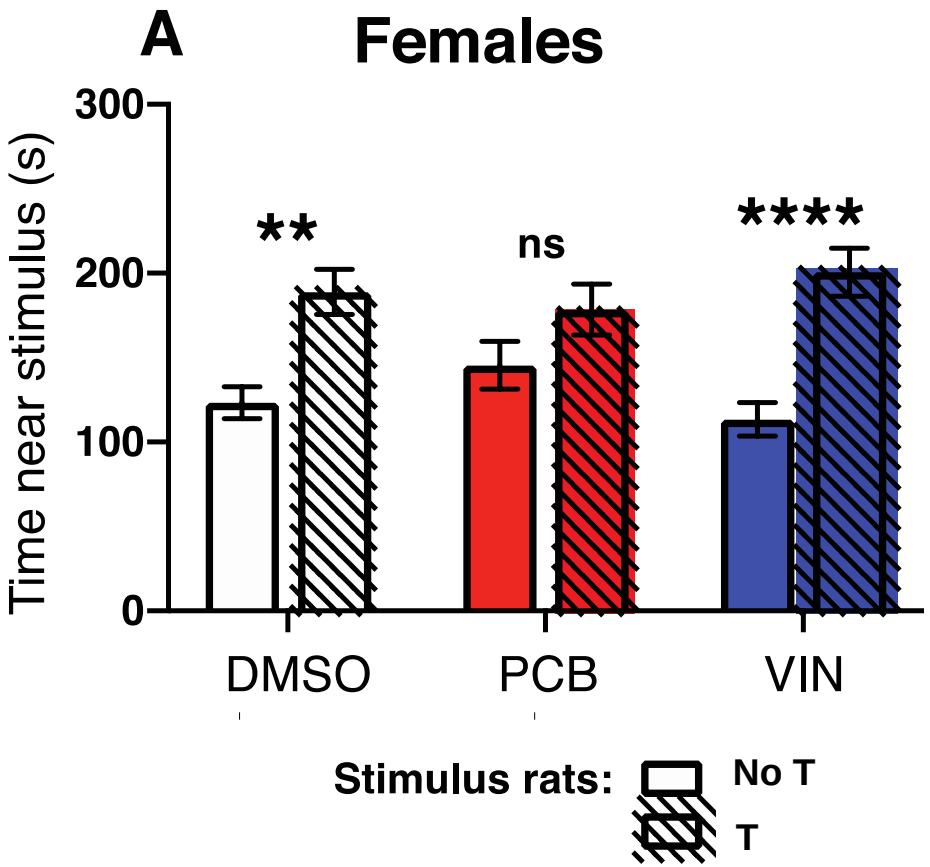


Male 2
(no T)



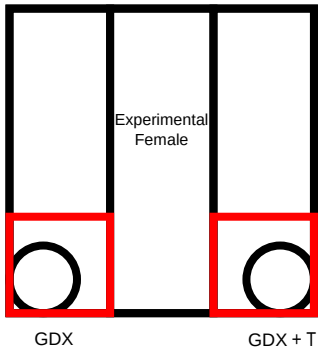
EDC treatment disrupts female mate preference



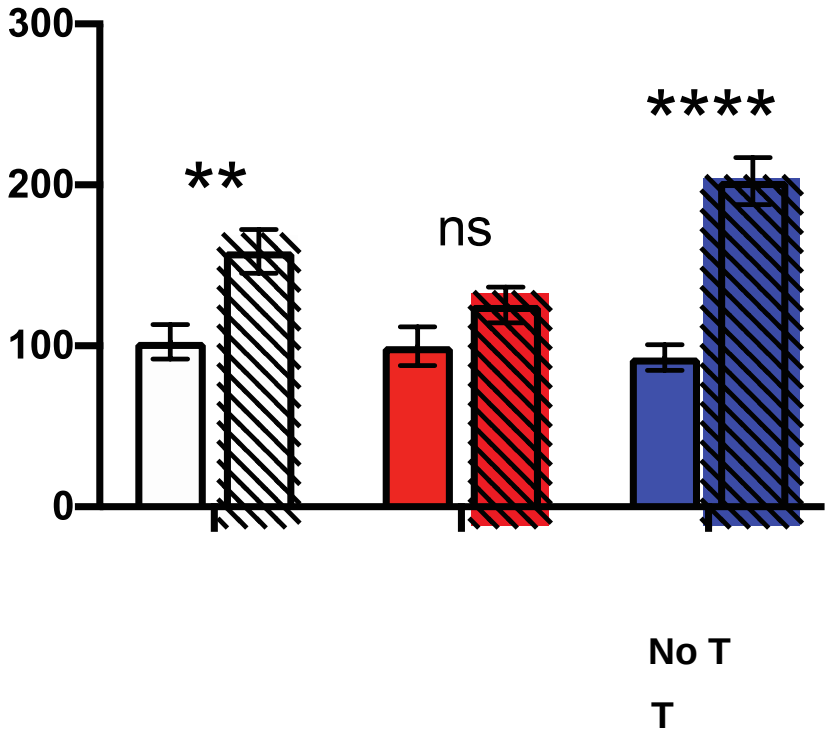


Hernandez Scudder... Gore, Endocrinology 161: bqaa124 (2020), doi: 10.1210/endocr/bqaa124

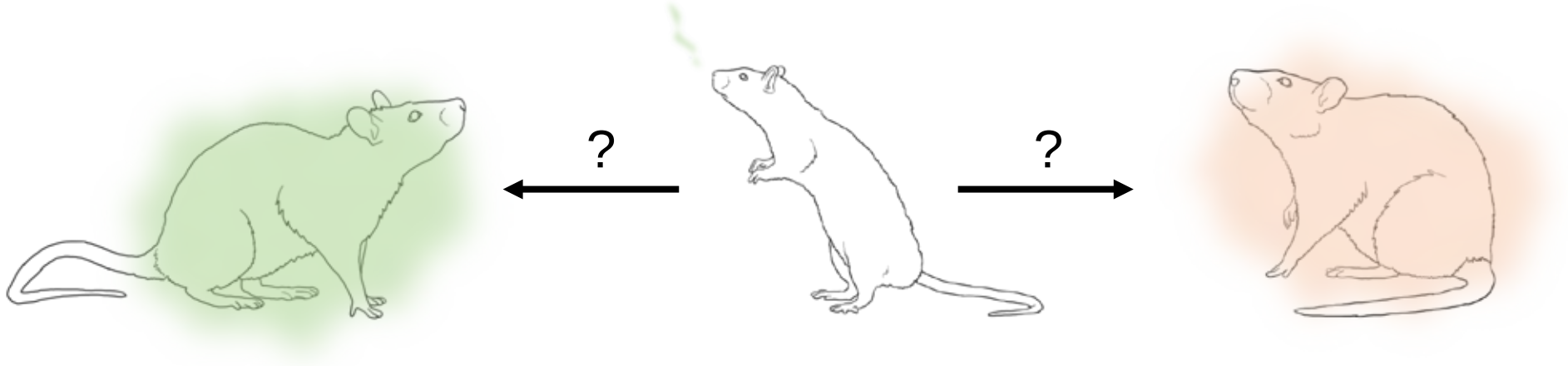
Deficits in odor preference explain disrupted mate preference



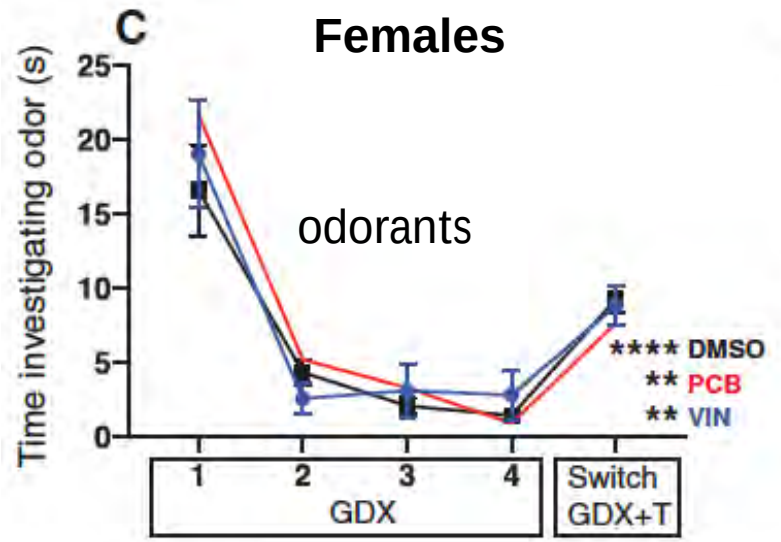
Urine-soaked filter paper



Does prenatal exposure to EDCs impair olfactory discrimination in adulthood?



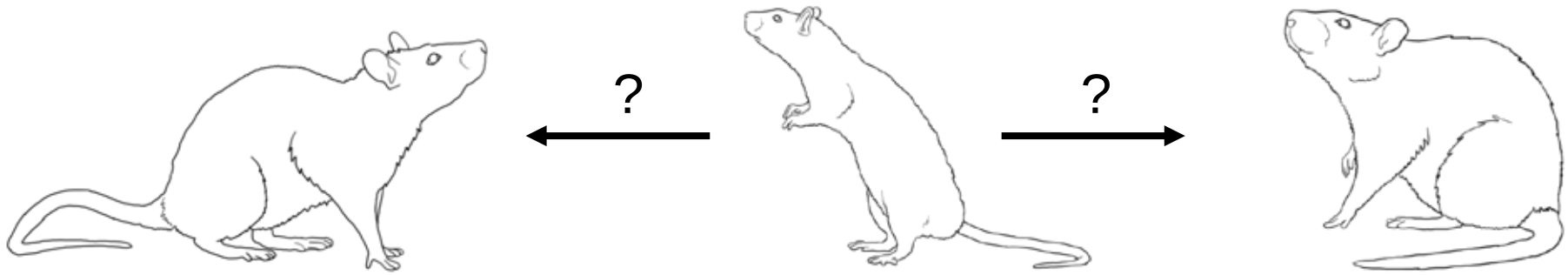
Habituation-Dishabituation



Hernandez Scudder *et al.*, Endocrinology 161: bqaa124 (2020), doi: 10.1210/endocr/bqaa124

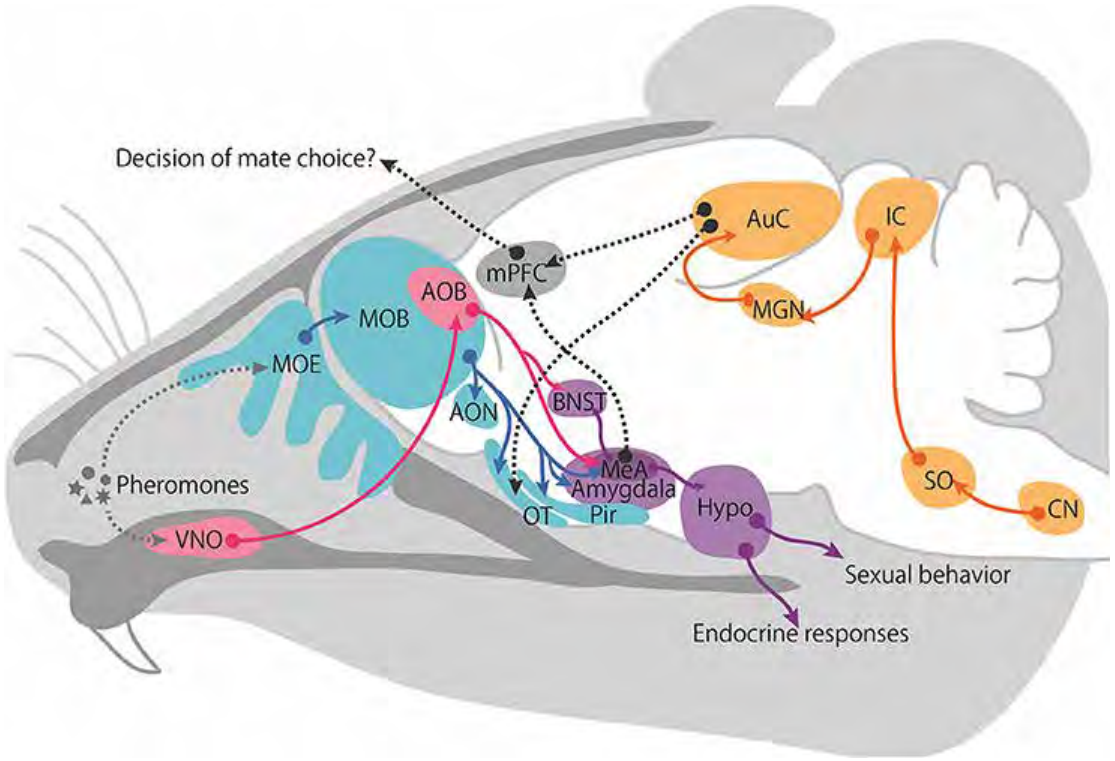
Summary (1)

Prenatal exposure to EDCs disrupts mate preference and odor preference behavior in adulthood, but not by means of impaired olfactory discrimination.



Sensory cues → Signal processing and decision making → Behavioral output

The effects of prenatal EDCs on olfactory processing



Hypothalamus: Ventromedial nucleus (VMNvl) and Preoptic area (POA)

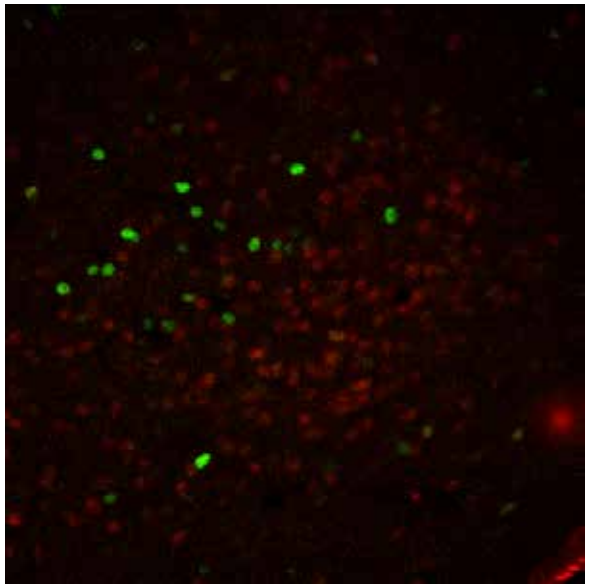
Piriform cortex (anterior, posterior)

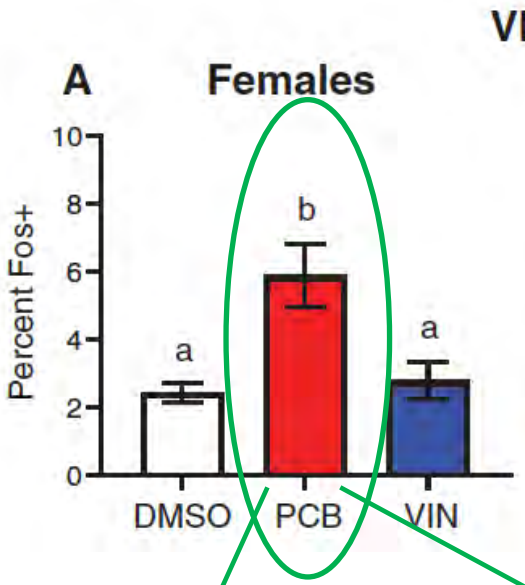
Medial amygdala (posterodorsal, posteroventral)

Fos immunoreactivity as a marker of neuronal activation 1 hr after the odor preference test

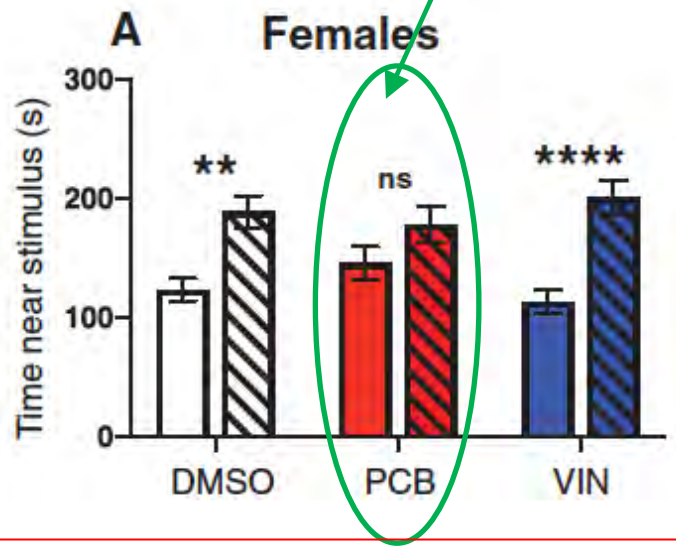
from Akari *et al.* Frontiers in Neuroscience, 2014.

The VMNvl is the only region affected by EDCs, and only in females

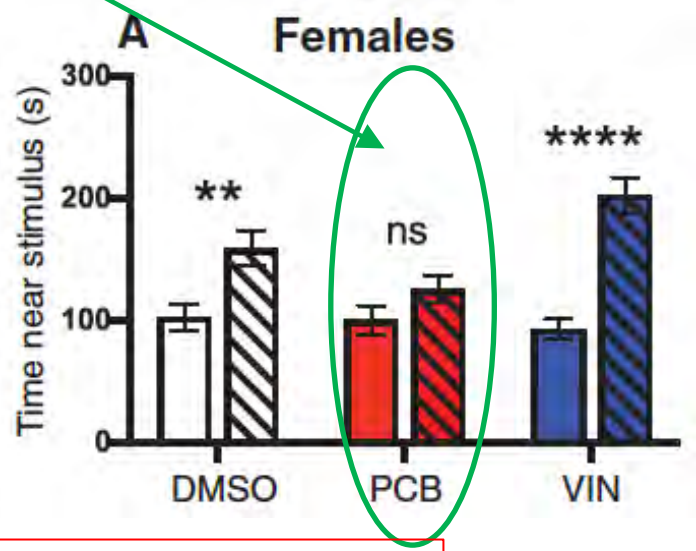




Mate Preference



Odor Preference



No treatment effect in POA, piriform cortex, amygdala.

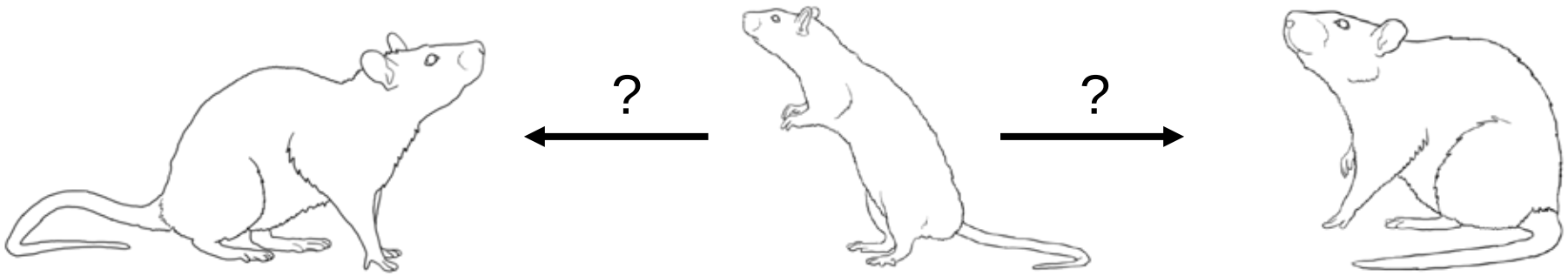
Sex difference in the cortex (F>M).

Hernandez Scudder *et al.*, Endocrinology 161: bqaa124 (2020), doi: 10.1210/endocr/bqaa124

Summary (2)

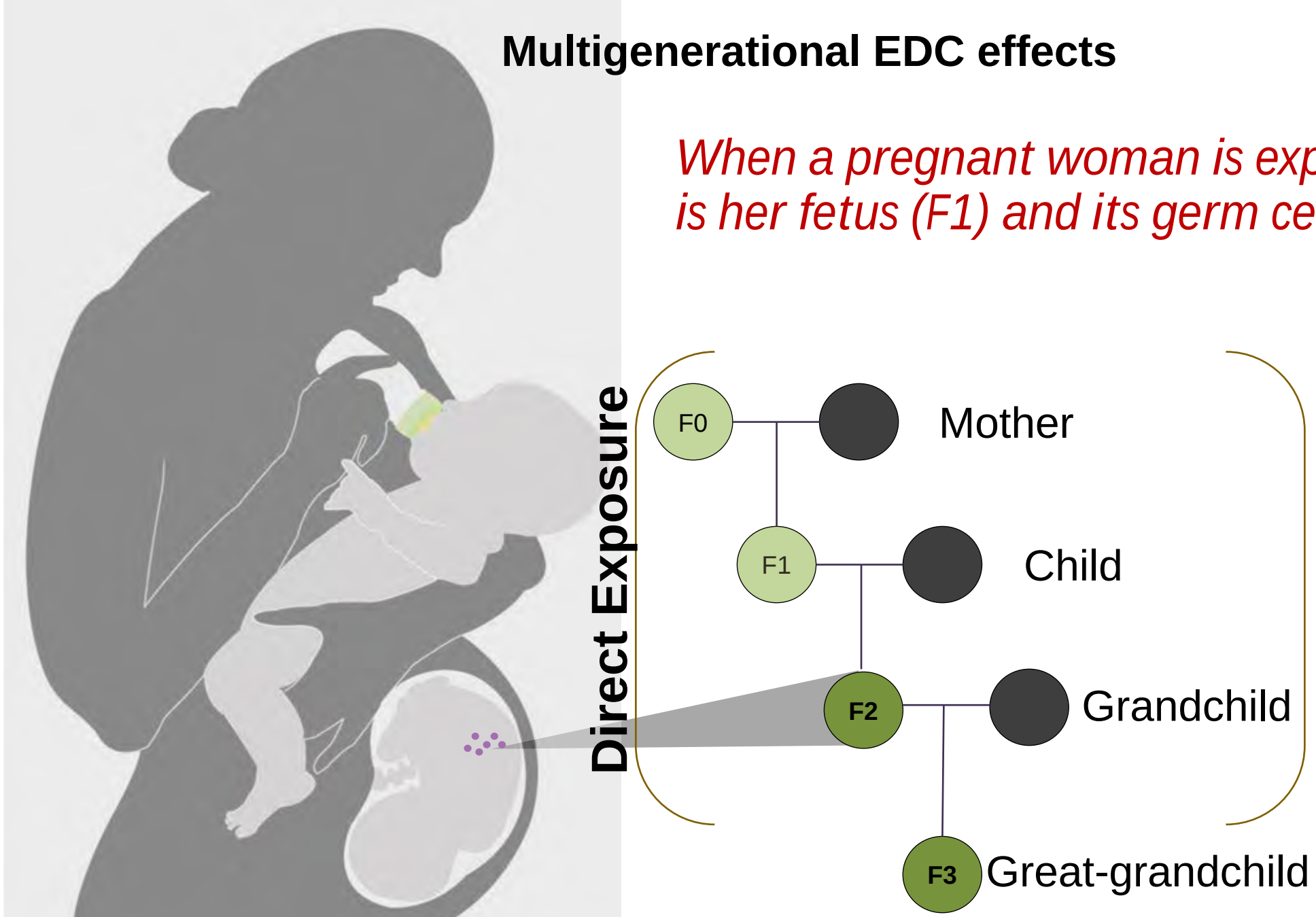
Prenatal exposure to EDCs disrupts mate preference and odor preference behavior in adulthood, but not by means of impaired olfactory discrimination.

Deficits in mate and odor preference behavior are associated with increased Fos activation in the VMNvl in females, but not males.



Multigenerational EDC effects

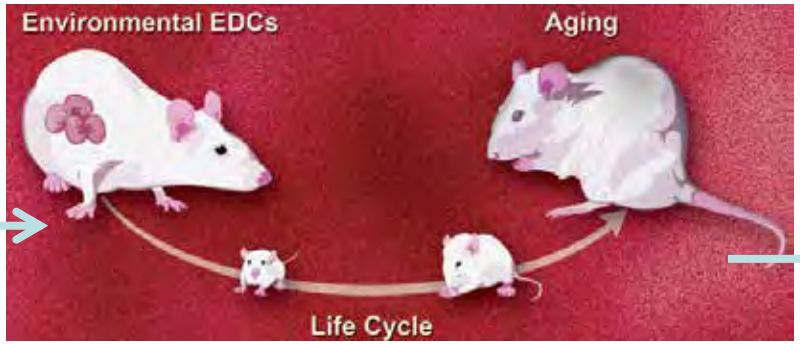
When a pregnant woman is exposed, so is her fetus (F1) and its germ cells (F2)



Gore & Patisaul, 2010

Multigenerational EDC Effects

Developmental exposure *in utero*



Future Generations

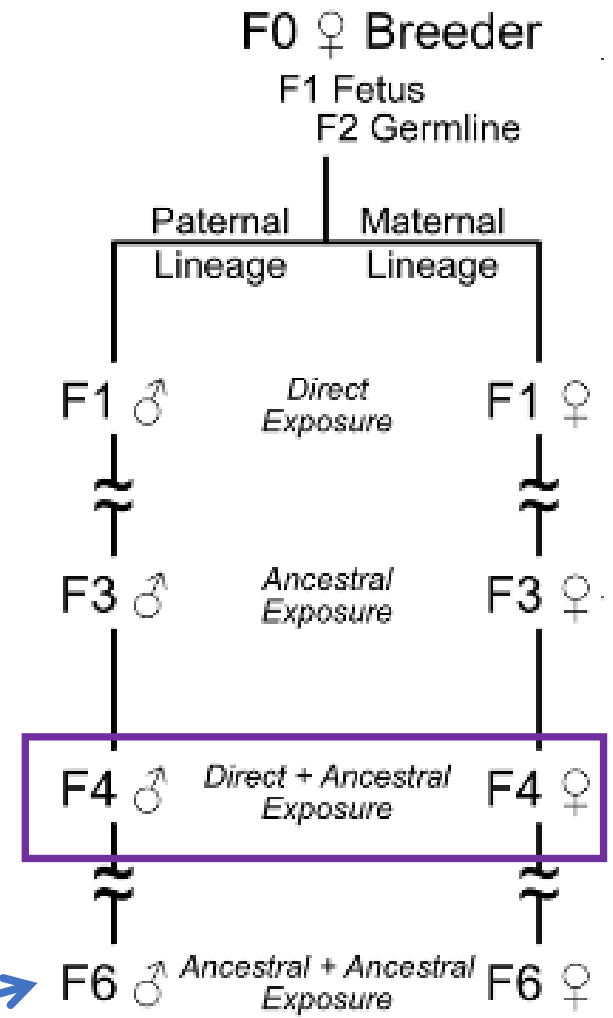
- Legacy vs. contemporary EDCs with different mechanisms
- Combination of direct and heritable effects
- Importance of lineages (maternal, paternal)
- Sex differences
- Epigenetic programming mechanisms

"Two hits of EDCs, 3 generations apart"

Two hits of EDCs 3 generations apart

Expose Prenatally
- DMSO vehicle
- PCBs (A1221)
- Vinclozolin

Expose Prenatally
- DMSO vehicle
- PCBs (A1221)
- Vinclozolin



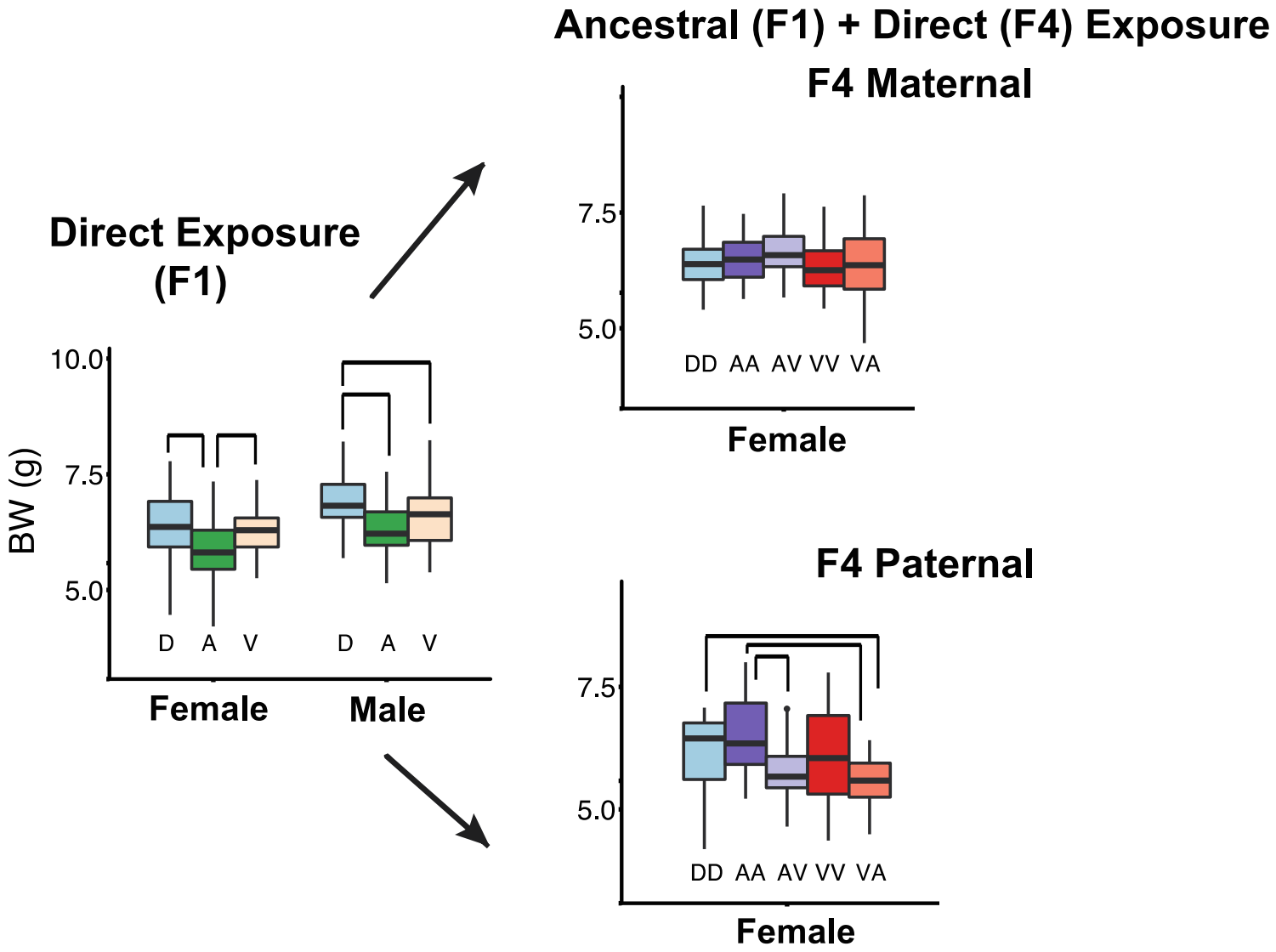
Direct Prenatal Exposures

Ancestral Exposures

Ancestral + Direct Prenatal Exposures

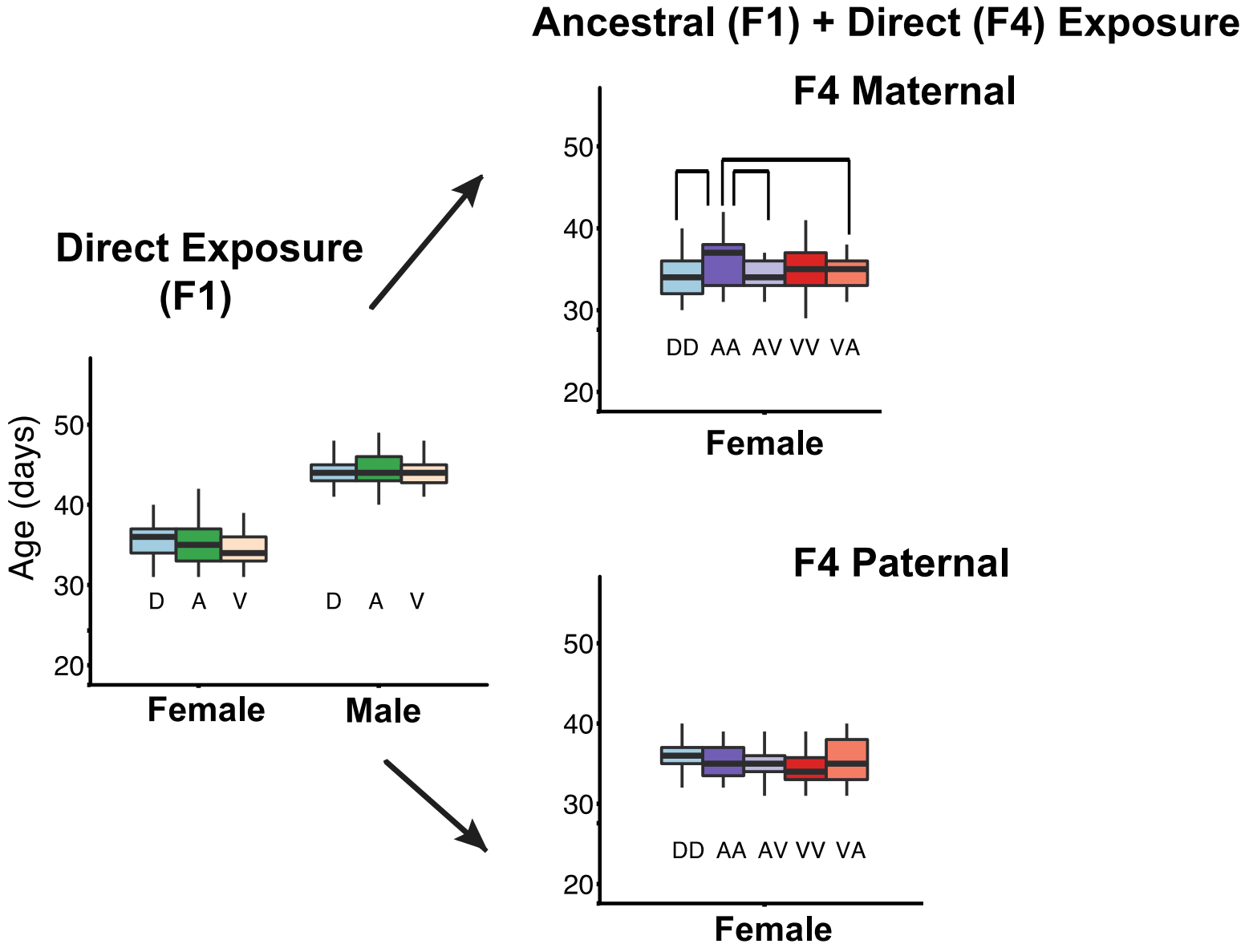
Double Ancestral Exposures

Body Weight on P1



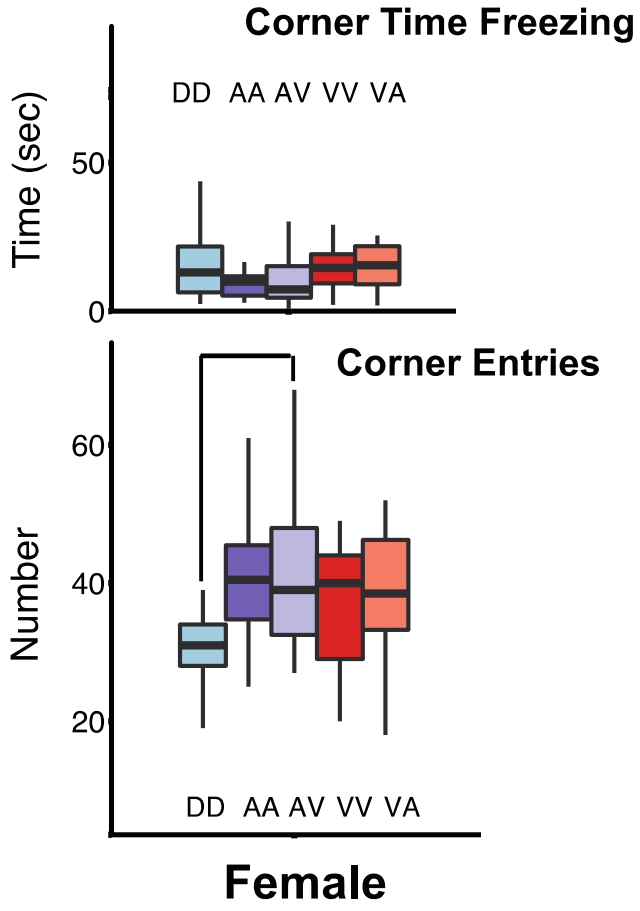
Ross Gillette, Lindsay Thompson, David Crews

Age at Puberty



Open Field (adult)

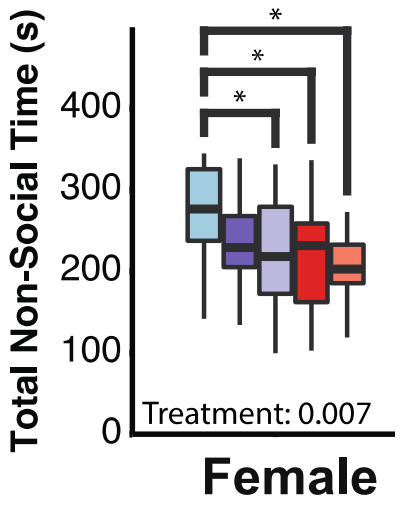
Ancestral (F1) + Direct (F4) Exposure
F4 Maternal



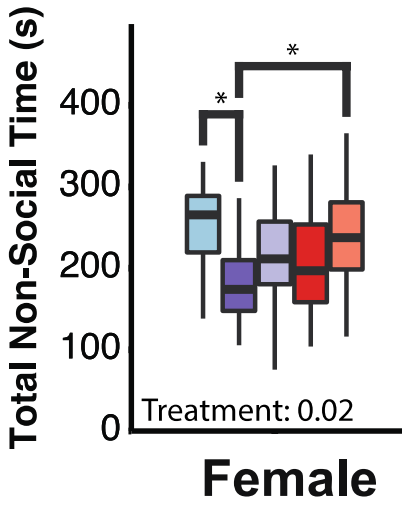
Social Interaction Dynamics (adult)

Ancestral (F1) + Direct (F4) Exposure

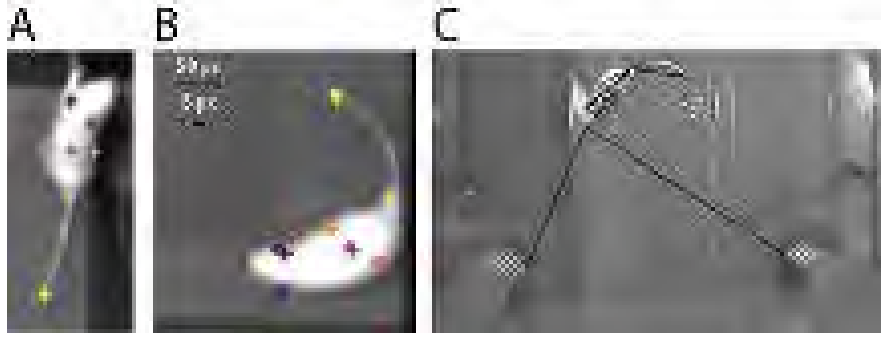
F4 Maternal



F4 Paternal



Dr. Ross Gillette



Gillette, Dias… Gore, Toxics 10: 30 (2022)

Summary (3) – “2 Hits of EDCs 3 Generations Apart”

- Each generation has a unique phenotype in response to EDC exposures.
  - *“Emergent phenotypes” caused by EDCs: there may be no F1 phenotype, but a phenotype emerges, especially after a 2nd hit in the F4 generation.*
- The nature of the second hit (same vs. different EDC) is a key determinant of the outcome.
  - *Ecological relevance: as new EDCs come onto the market, this is overlaid on our historical exposures.*
- Virtually all outcomes, in all generations, were sexually dimorphic.
- Lineage was a key determinant in outcomes.

Take-home messages and Future directions

EDCs affect women's health: this includes reproductive health, as well as other endocrine and neurological domains.

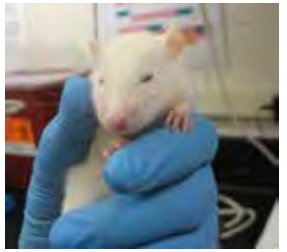
Sex differences are common for EDC effects, underscoring the importance of including females in all studies.

Individuals experience multiple environmental perturbations throughout their life histories such as EDCs and other stressors. The combination of these experiences shapes the individual's phenotypes.

Ancestral epigenetic processes add to the complexity by shaping the response to current and future environmental challenges. This is modeled in the "2 hit, 3 generations apart" paradigm.

Our future direction is to pursue how the transfer of epigenetic information from germline to somatic tissues such as the brain can happen, and result in neurobehavioral changes.

Thank you!



Our happy rats

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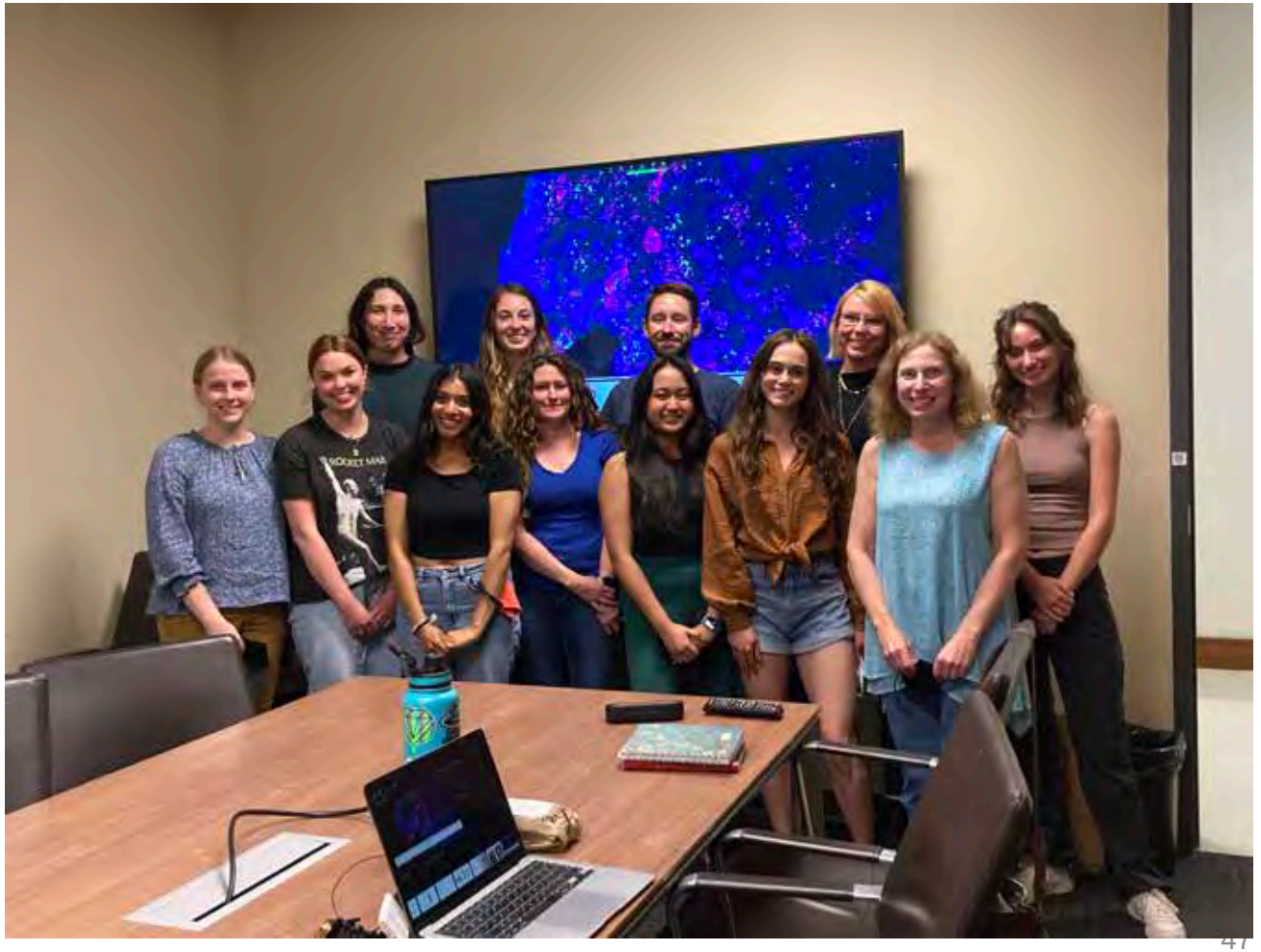
Dr. Ross Gillette
Dr. Emily Hilz
Lindsay Thompson
Madeline Streifer
Dana Sheinhaus

Collaborators:
Dr. David Crews

Everyone else in the Gore Lab, but especially our wonderful undergraduates



NIH Research Panel

Anne Marie Jukic, Ph.D., Francesco DeMayo, Ph.D.,
Carmen Williams, M.D., Ph.D., Janet Hall, M.D., M.S.

Moderated by Keiva Nelson

NIH Research Panel

Anne Marie Jukic, Ph.D.

Investigator, Fertility and Reproductive Health Group

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SCAN ME

We're hiring! Postdoctoral fellowships are available:
https://www.training.nih.gov/postdoc_jobs_nih/view/_31/9294/NIEHS_FRH_PD

NIH Research Panel

Francesco DeMayo, Ph.D.

Chief, Reproductive and Developmental Biology Laboratory

National Institute for Environmental Health Sciences

Molecular Analysis of Uterine Function

Francesco DeMayo Ph.D.

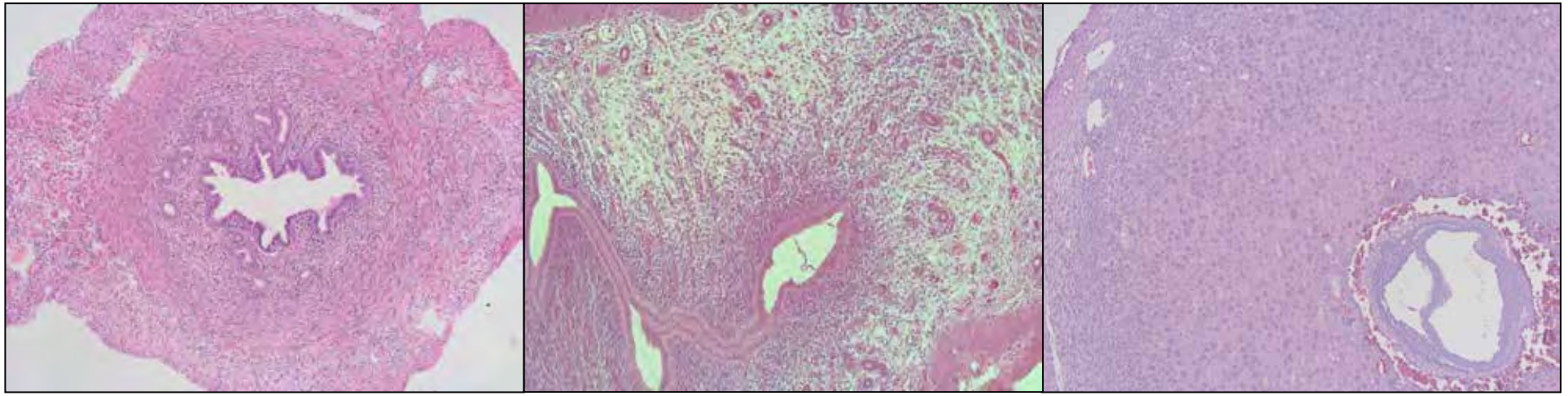
Endocrine Disrupting Chemicals and Women's Health Symposium
Virtual
July 18-19, 2023

Environment and the Female Reproduction

- The female reproductive tract is the most sensitive organ to endocrine signaling.
- Dysfunctions of the uterus such as Infertility, Endometriosis, Endometrial Cancer, Fibroids and Preterm Birth may be the result of hormone deregulation.
- Endocrine disruptors, stress, inflammation and diet can result in infertility, preterm birth and impairment of women's health.

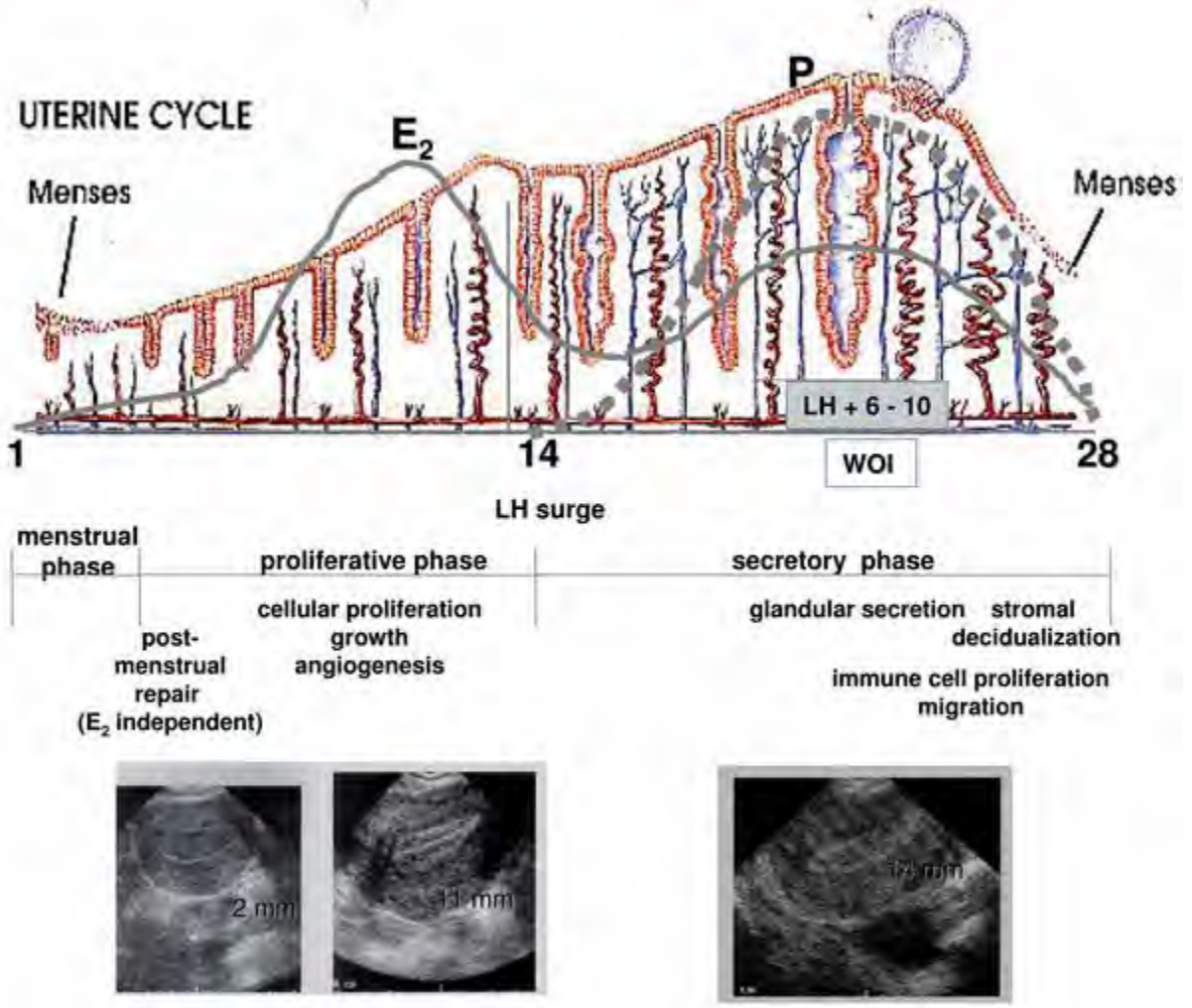
Rashtian et al., 2019 Reprod. Biol and Endo., Bala et al., 2020 Reprod. Sci

The Uterus Undergoes Dynamic Changes During Pregnancy



Nonpregnant Uterus | Peri-implantation Uterus | Decidualized Uterus

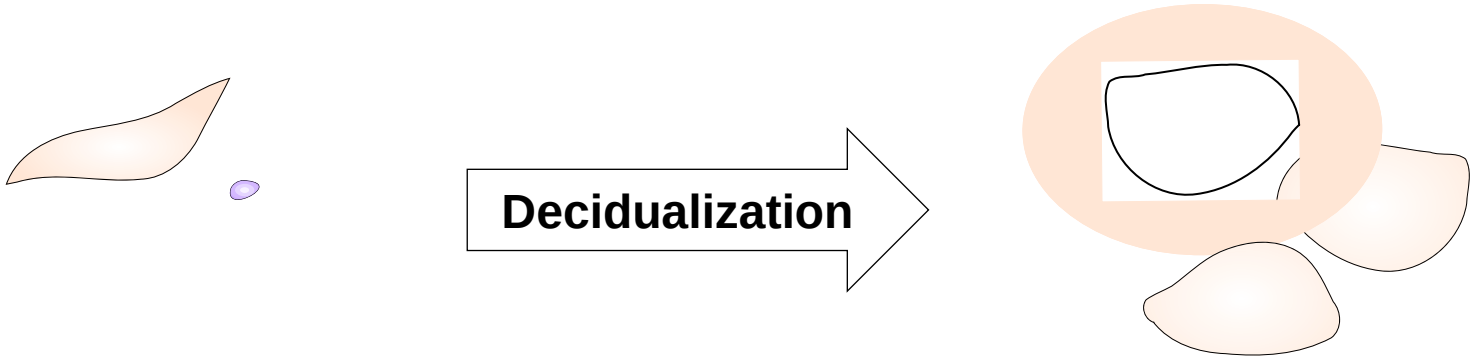
Changes in the human uterus during the Menstrual cycle.



Giudice, Reproductive Biology and Endocrinology (2006) 4(Supp 1):84

Decidualization

- **Endometrial stromal cells differentiate into decidual cells, which serve several functions during early pregnancy:**
  - **Support embryo**
  - **Regulate trophoblast invasion**
  - **Enhance vascularization**
  - **Modulate maternal immunity**



Human endometrial stromal cells (HESCs)

Decidual cells

Regulation of Human Endometrial Stromal (HES) Cell Decidualization

Isolate primary HES cell from 3 different patients

↓

Induce Decidualization
(50 mM db-cAMP, 10nM E2, 1mM MPA)

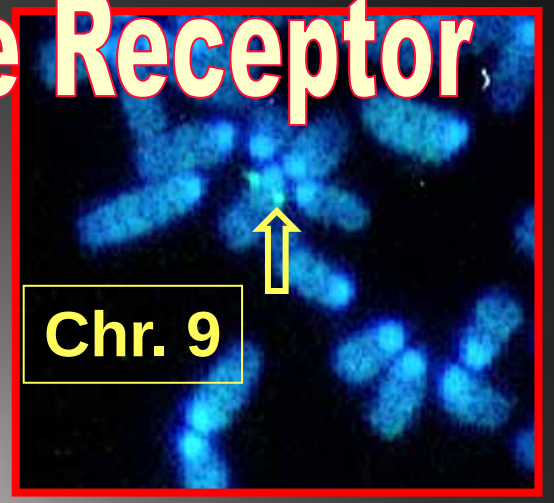
↓

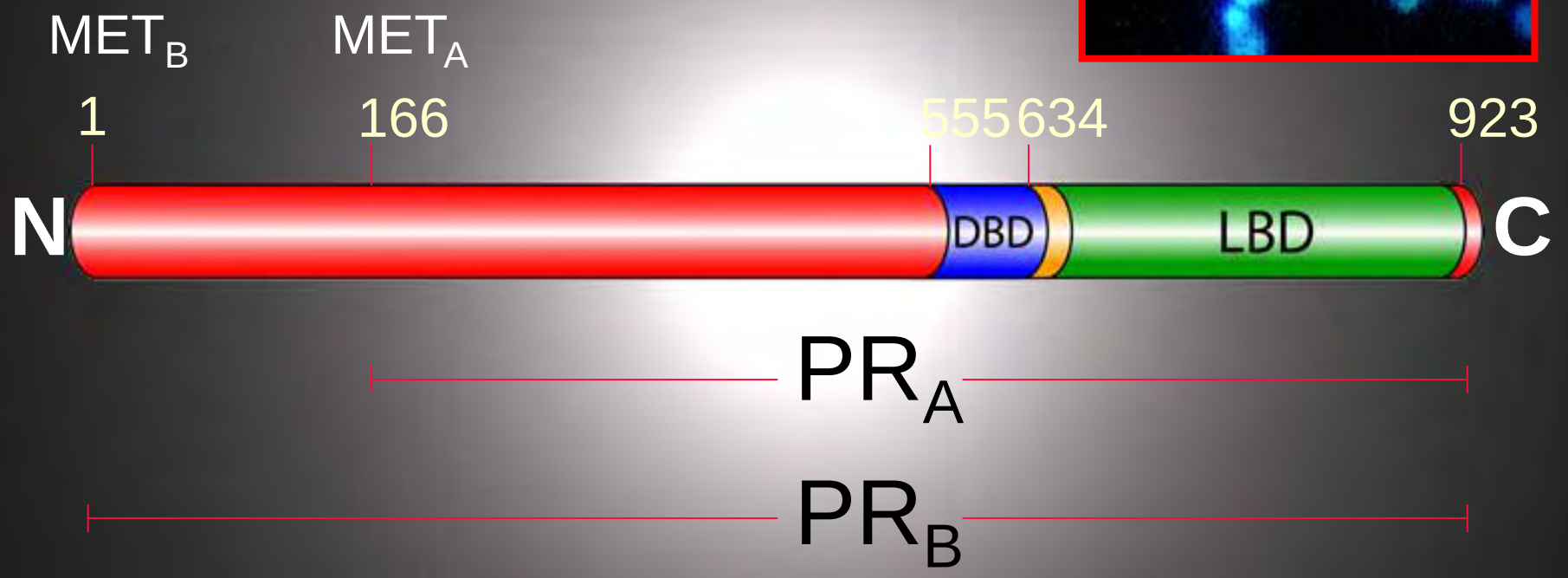
Change in morphology and increased expression of marker proteins IGFBP1 and PRL

Progesterone: the Hormone of Pregnancy

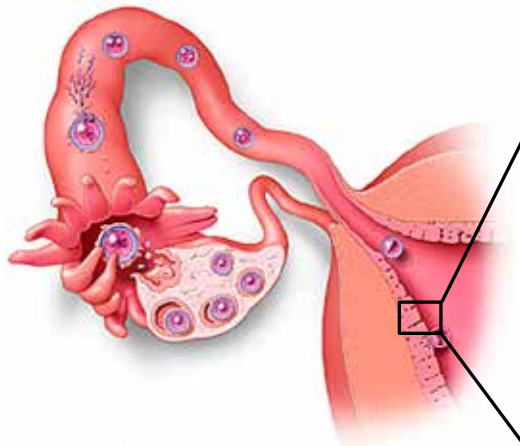
- Progesterone acts through its cognate receptors PGRA and PGRB.
- Regulates the timing of the embryo transport to the site of implantation.
- Negates the mitogenic actions of Estrogen on uterine epithelium.
- Integral part of the paracrine cross talk between epithelium and stroma that regulates uterine function.
- Regulates the ability of the uterus to support embryo invasion and growth.
- Regulates myometrial quiescence and parturition.
- **Regulates the “Window of Receptivity”.**

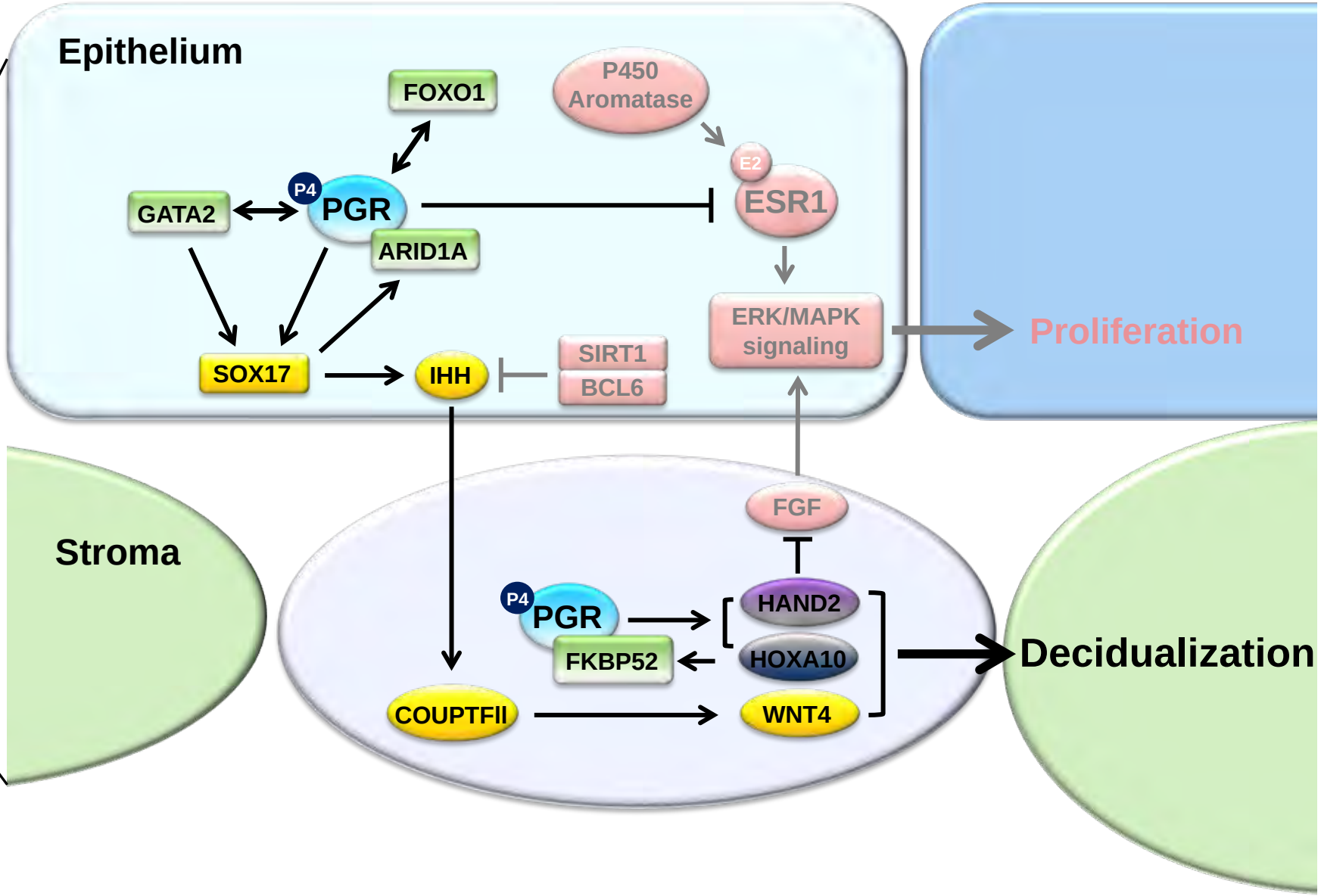
The Murine Progesterone Receptor





Progesterone Receptor (PGR) Function in the Receptive Endometrium





Marquardt et al., *IJMS*. 2019

Serum Response Factor (SRF) as a Potential PGR Co-regulator in the Uterus

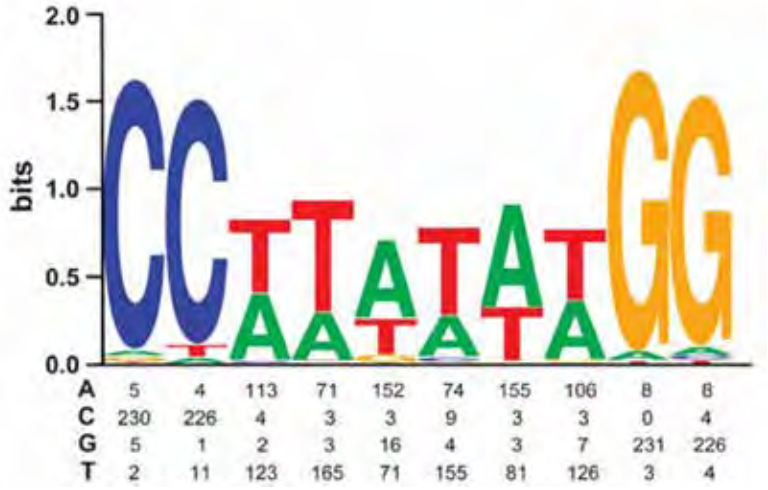
The **SRF binding motif (CArG) is enriched in PGR binding intervals** in term pregnant and non-pregnant human myometrial samples based on PGR ChIP-seq

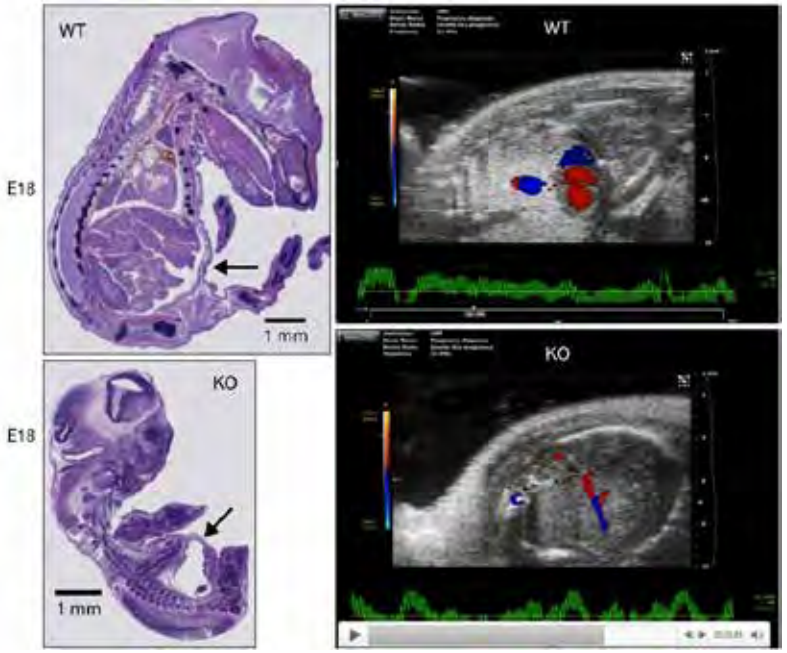
Motif		Log *p*-value of enrichment	
		NP	TP
	PGR	-225.8	-1445
	CArG	-127.1	-66.32

NP: nonpregnant myometrial tissue
TP: term pregnant myometrial tissue

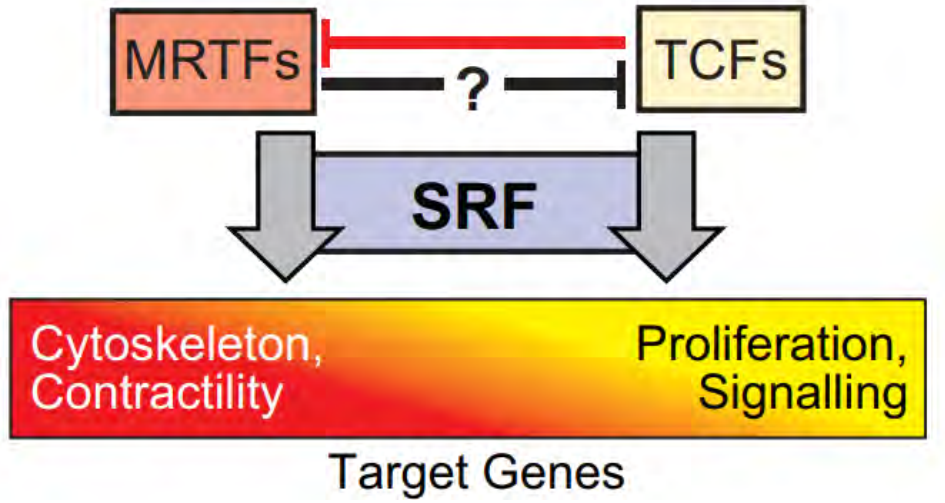
Wu et al., *FASEB J*. 2020

SRF Molecular Function





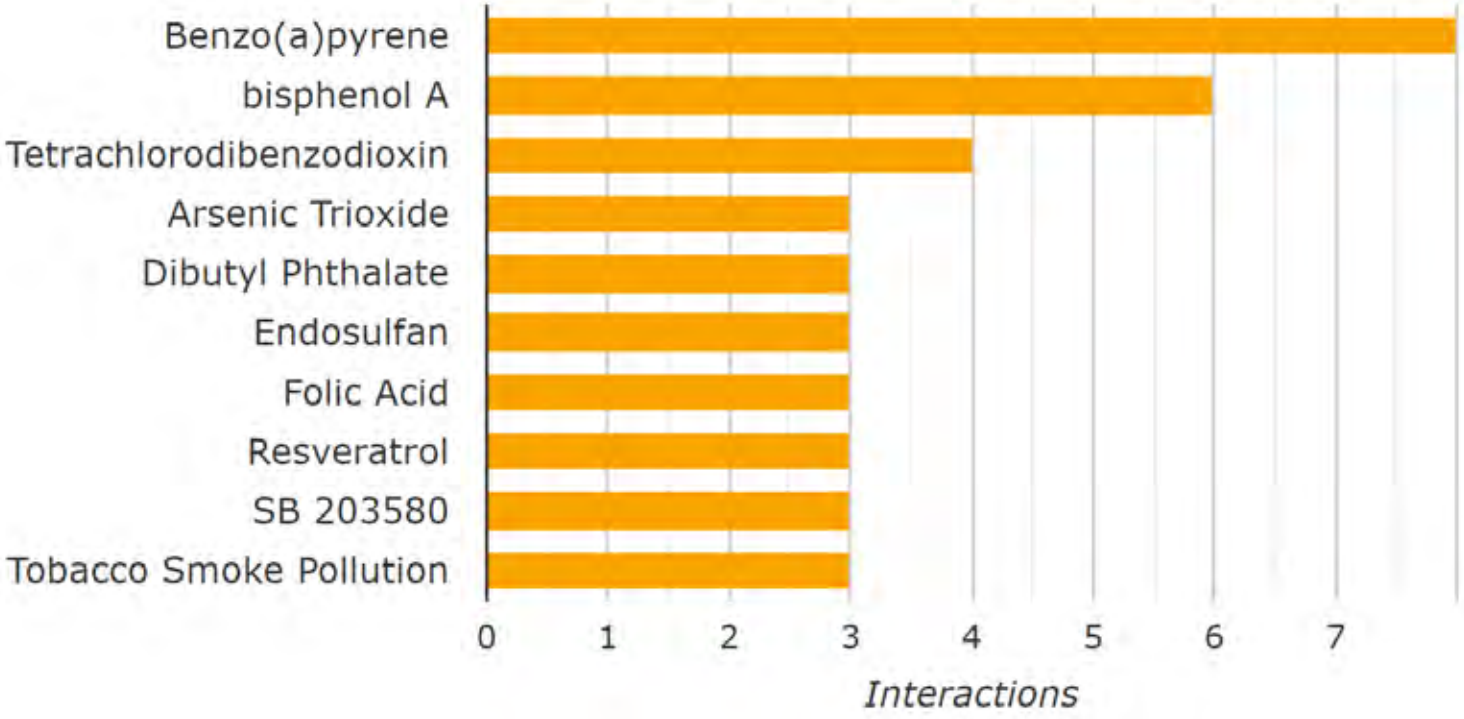
- Widely-expressed transcription factor from the “MADS-box” protein family (Miano, 2010).
- Binds a consensus DNA element CC(A/T-rich)$_6$GG, referred to as the “CArG box” (Miano, 2010).
- Essential for prenatal development of the GI tract and heart (Park et al., 2015).
- Transcriptional output is determined by its cofactors (Gualdrini et al., 2016).



Miano, *Lab. Invest.* 2010; Park et al., *J. Neurogastroenterol. Motil.* 2015; Gualdrini et al., *Mol. Cell* 2016

SRF and the Environment

Top Interacting Chemicals (10/81)



40% (32/81) of known SRF-interacting chemicals also interact with PGR.

Illuminating how chemicals affect human health.

Comparative Toxicogenomics Database

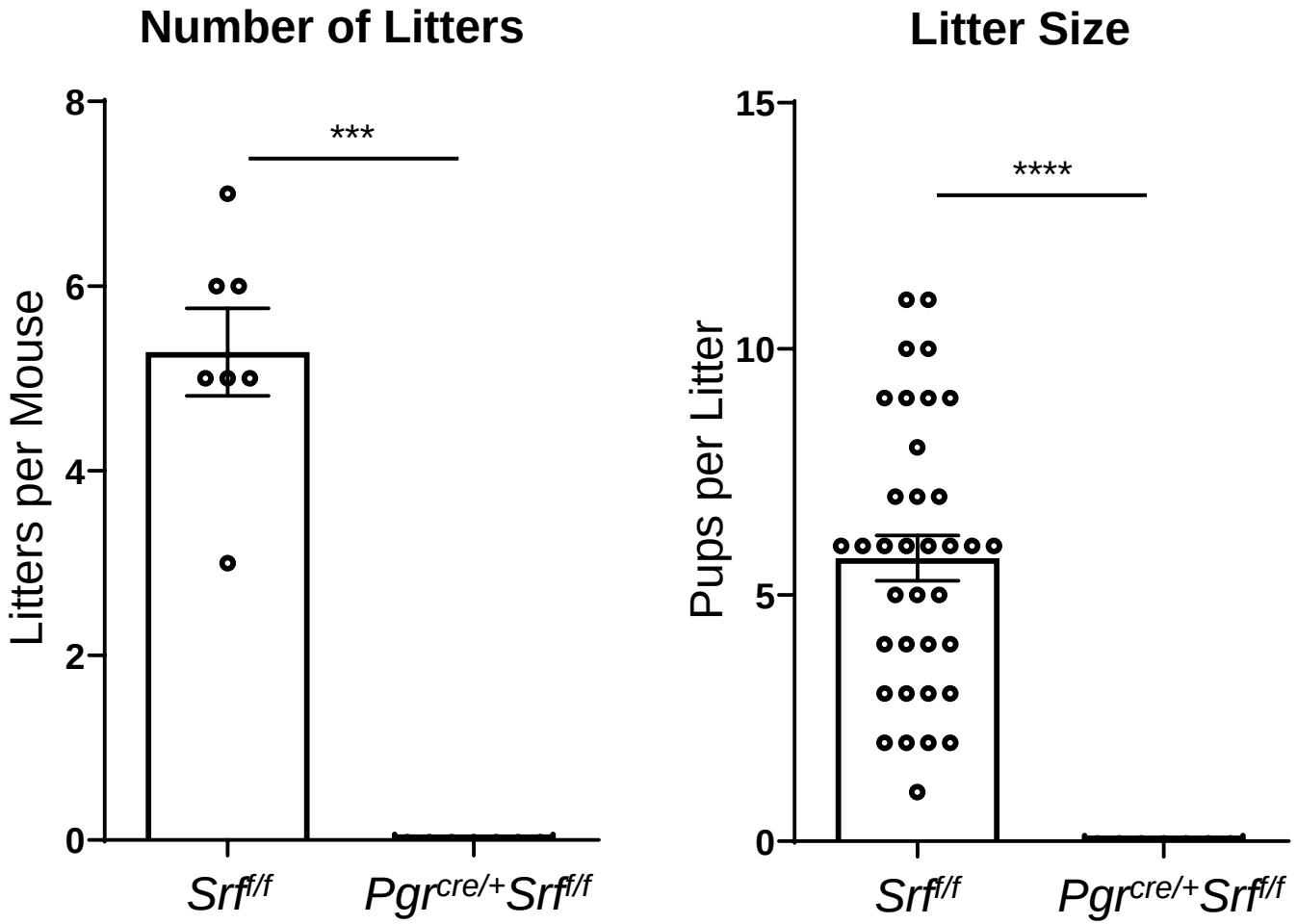
ctdbase.org; wordclouds.com

Hypothesis:

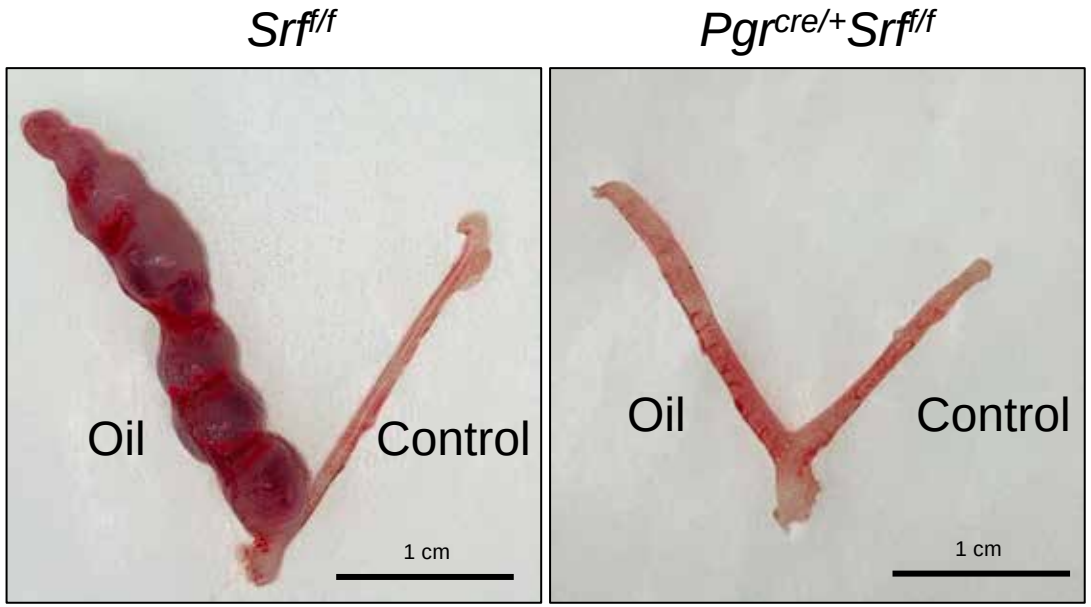
SRF collaborates with PGR to regulate the transcriptional environment needed for uterine function.

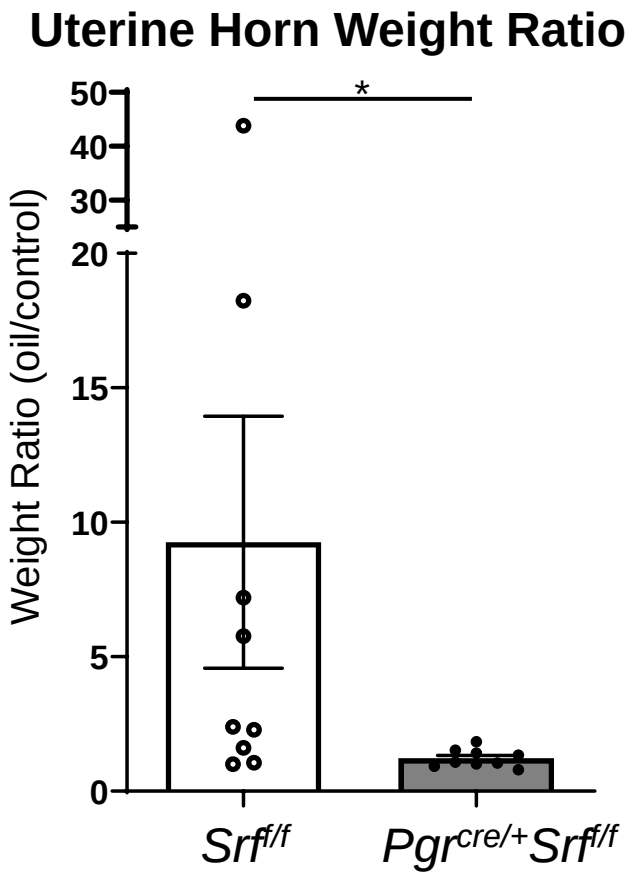
Pgr$^{cre/+}$*Srf*$^{f/f}$ Females are Infertile

Six-Month Fertility Trial



SRF Loss Results in a Decidualization Defect in *Pgr*$^{cre/+}$*Srf*$^{f/f}$ Mice

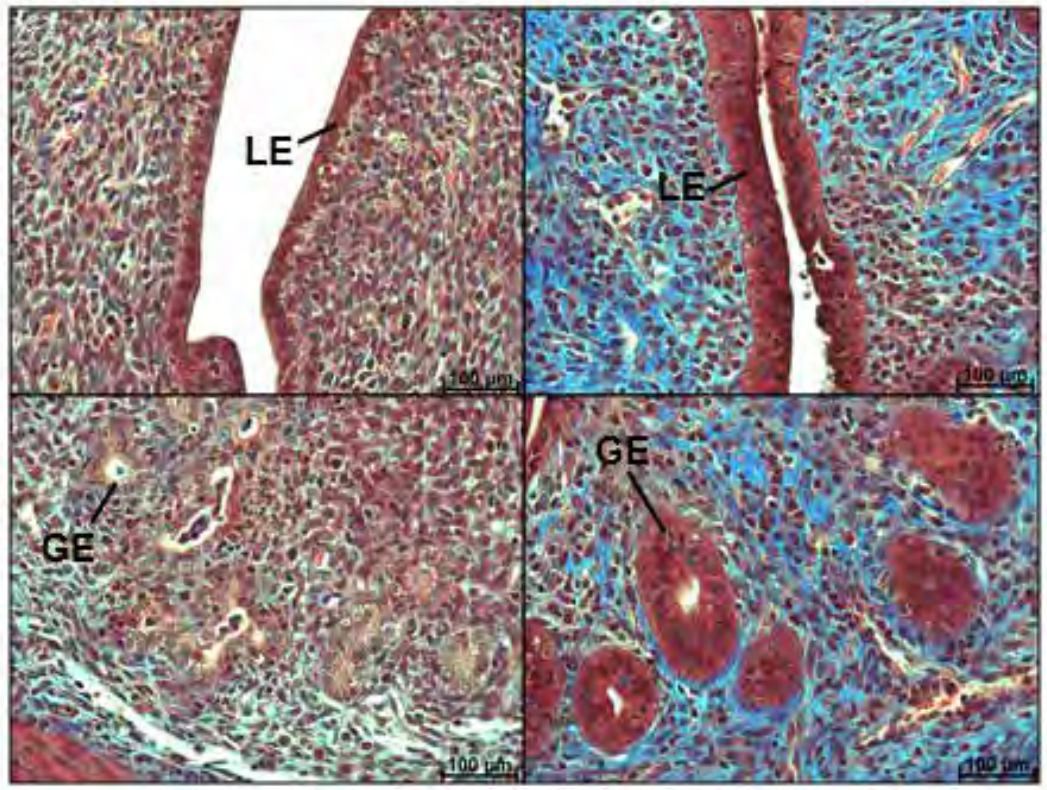




SRF Loss Results in Uterine Fibrosis in *Pgr*$^{cre/+}$*Srf*$^{f/f}$ Mice

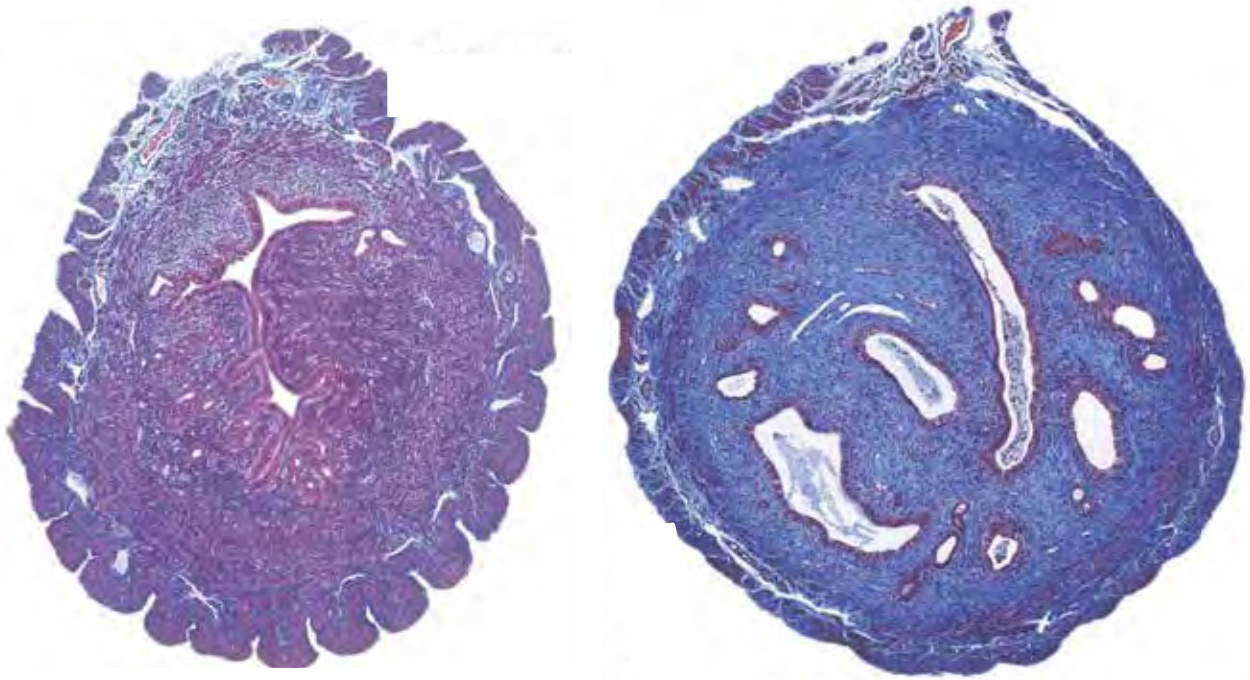
11-Week Old Uterus (Masson Trichrome)

Srf$^{f/f}$ *Pgr*$^{cre/+}$*Srf*$^{f/f}$



Post Breeding Trial Uterus (Masson Trichrome)

Srf$^{f/f}$ *Pgr*$^{cre/+}$*Srf*$^{f/f}$

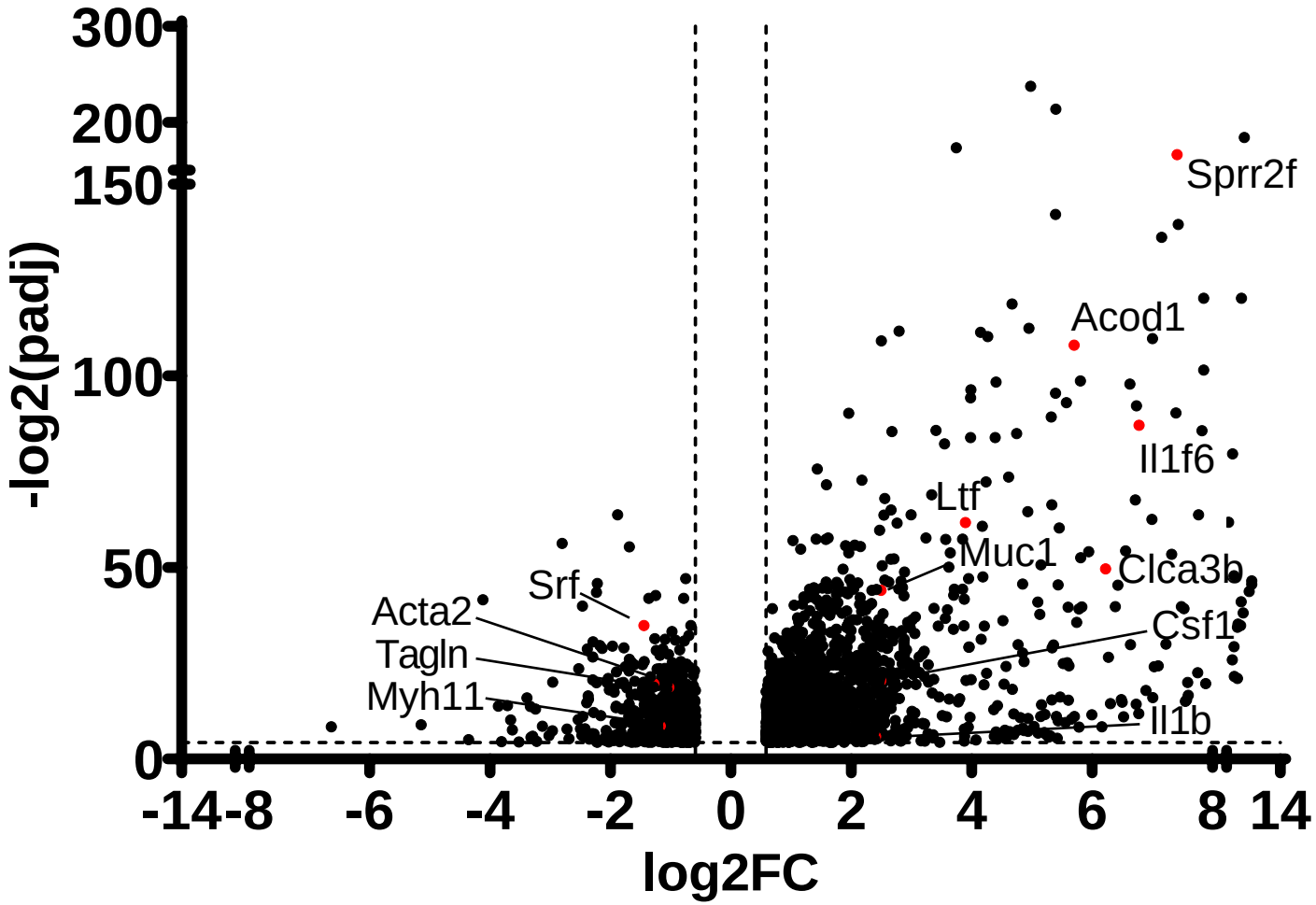


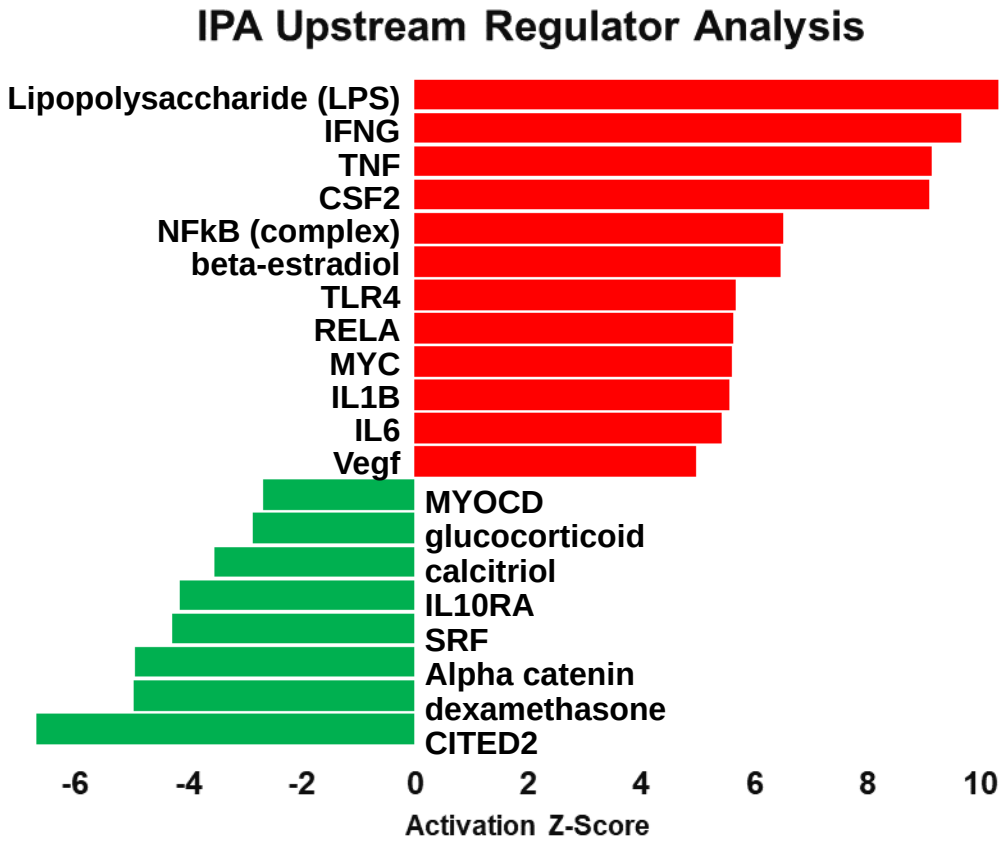
Olivia Emery

Hormone-independent Effects of SRF Loss on Uterus

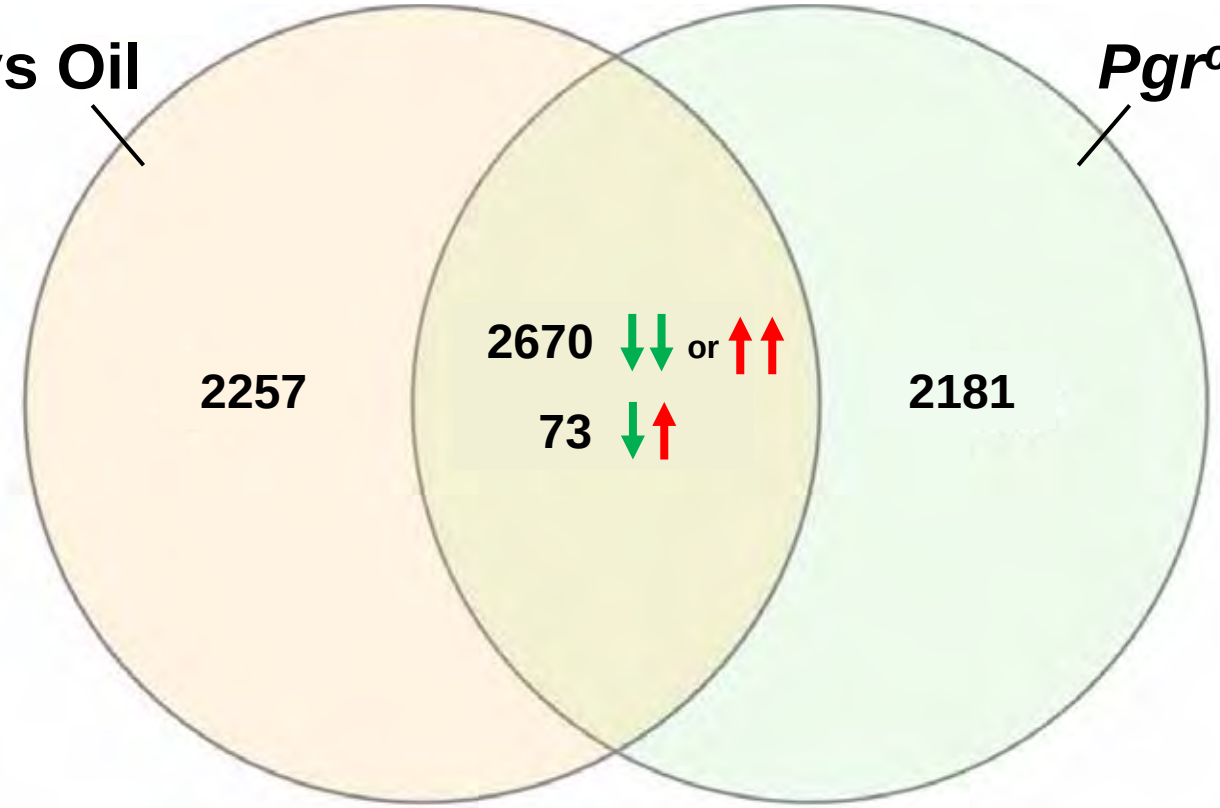
Oil-treated *Pgr*$^{cre/+}$*Srf*$^{f/f}$ vs Oil-treated *Srf*$^{f/f}$

2593 DEG (Padj<0.05; [FC]>1.5): 1635 ↑ 958 ↓



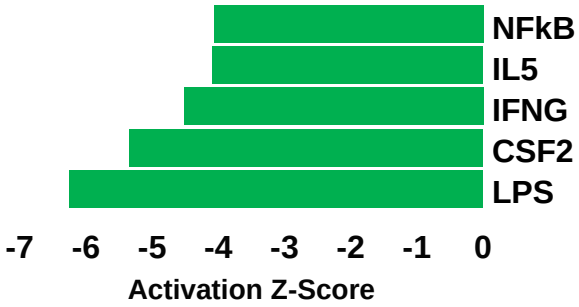


SRF Loss Switches P4 Response to Pro-Inflammatory



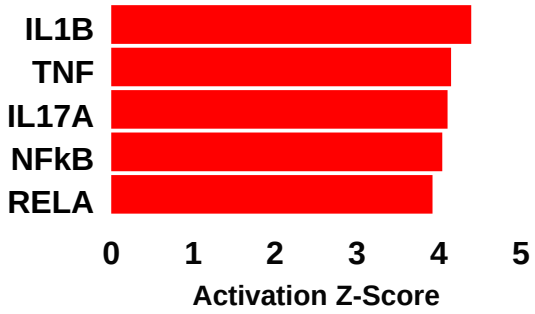
Loss of induction (2257)

Upstream Regulators



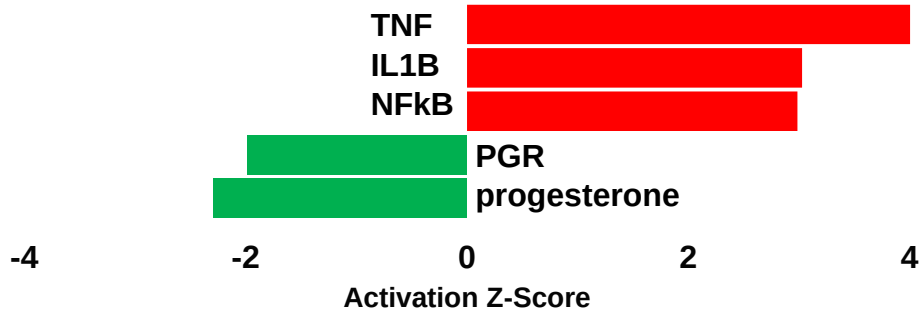
Gain of induction (2181)

Upstream Regulators



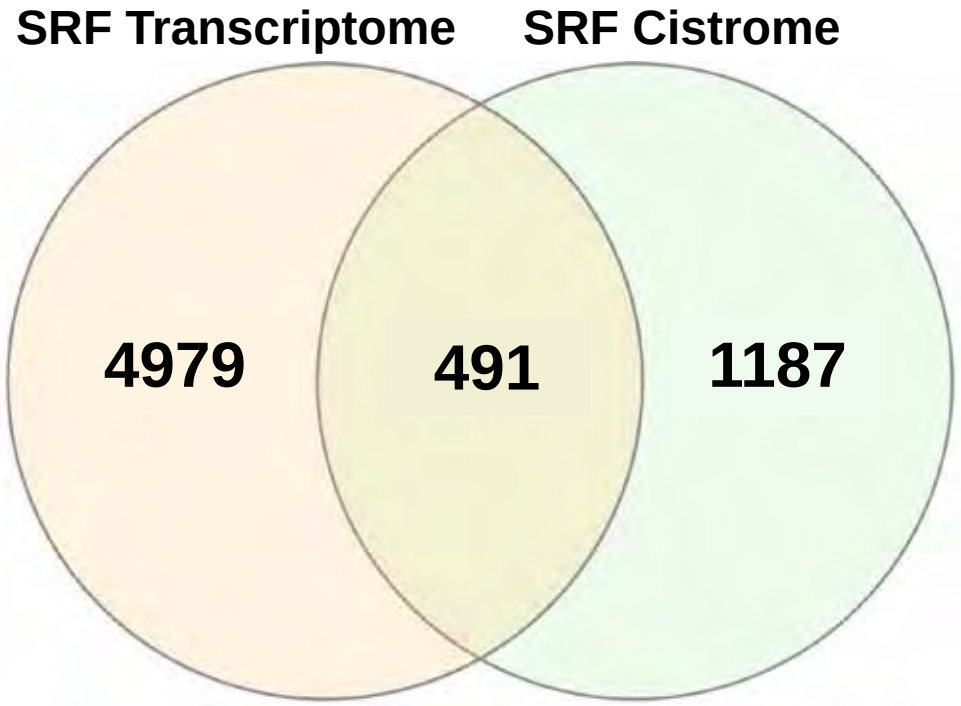
Opposite induction (73)

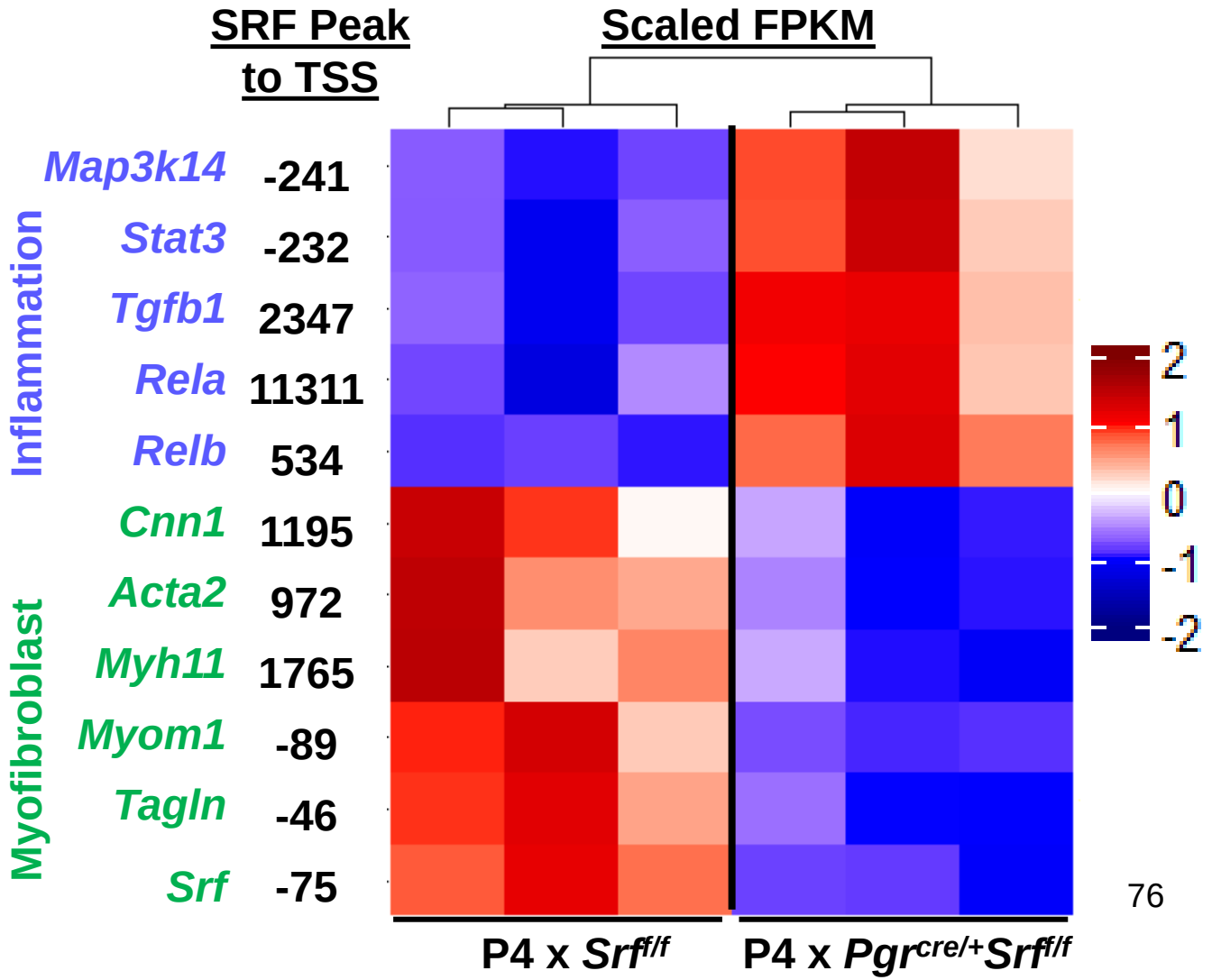
Upstream Regulators



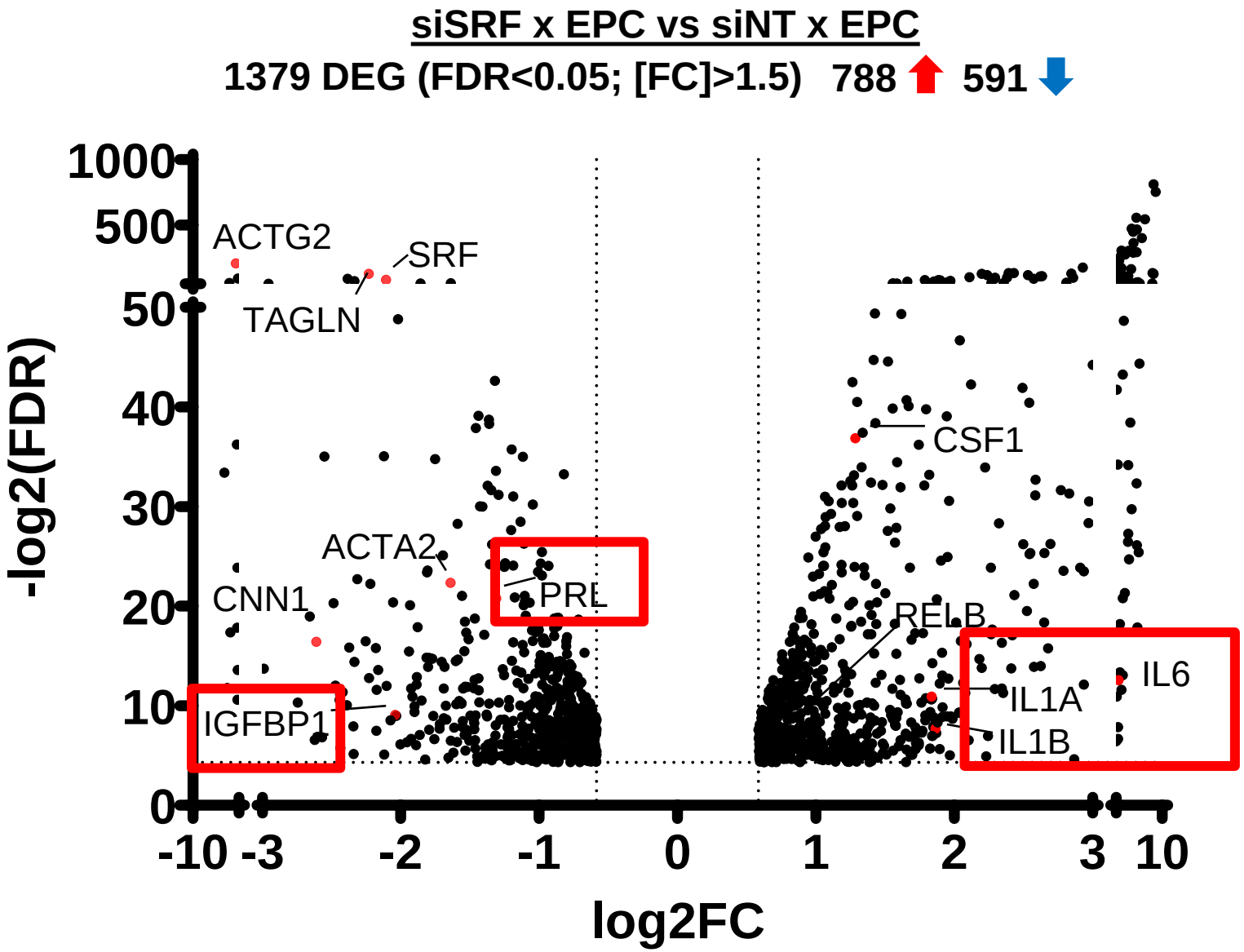
DEG = Padj<0.05; [FC]>1.5

Putative Direct SRF Target Genes in the P4-Treated Uterus





Decidualization Attenuated and Inflammatory Markers Upregulated after *SRF* Knockdown in Primary HESCs



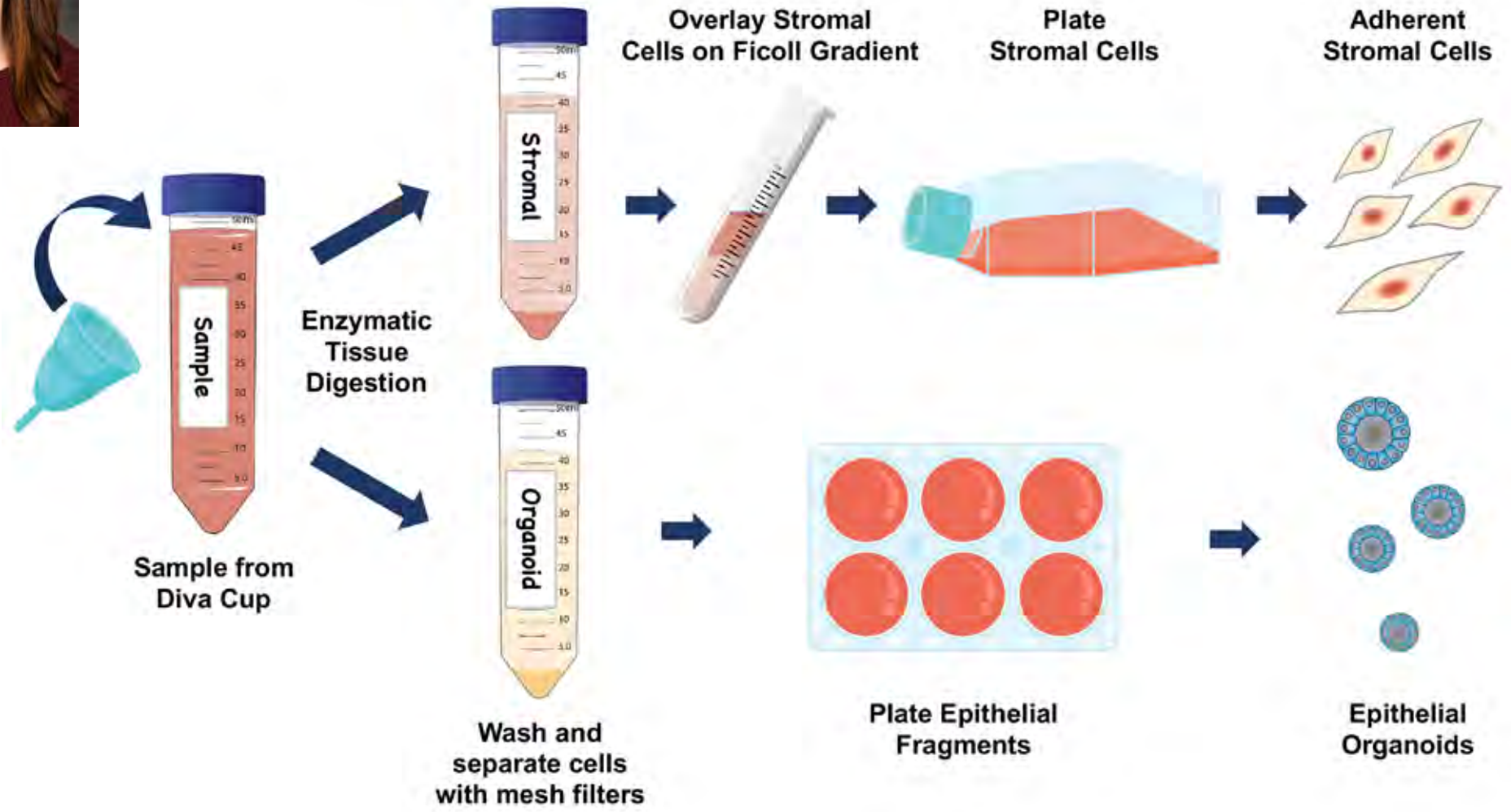
Decidualization Attenuated and Inflammatory Markers Upregulated after *SRF* Knockdown in Primary HESCs

Ingenuity Canonical Pathway	siSRF vs siNT EPC HESC (z-score)	P4 responsive Srf f/f only (z-score)	P4 responsive PRcre/+ Srf f/f only (z-score)	Opposite P4 response in PRcre/+ Srf f/f (z-score)
Pathogen Induced Cytokine Storm Signaling Pathway	4.276	-5.431	2.469	2.646
Macrophage Classical Activation Signaling Pathway	3.053	--	1.528	2.236
Crosstalk between Dendritic Cells and Natural Killer Cells	2.333	-3.207	--	--
IL-17 Signaling	2.236	--	2.558	2.236
TNFR1 Signaling	1.633	--	2.121	--
TNFR2 Signaling	1.633	--	2.236	--
Acute Phase Response Signaling	1.279	-2.683	3.71	2.236
Toll-like Receptor Signaling	1.155	-1.265	2.121	--
IL-8 Signaling	1.069	-2.121	1.807	--
IL-6 Signaling	0.894	--	3.9	--
STAT3 Pathway	0.632	-2.673	--	--
Macrophage Alternative Activation Signaling Pathway	0.471	-3.812	0.408	0.447
IL-10 Signaling	-2.065	0.816	-2.065	-0.816

Summary

- SRF is for female mouse fertility.
- SRF regulates the hormone regulated uterine decidual response.
- SRF loss results in uterine fibrosis.
- SRF is critical for human endometrial stroma decidualization.
- SRF loss promotes inflammatory pathways in mouse and humans.

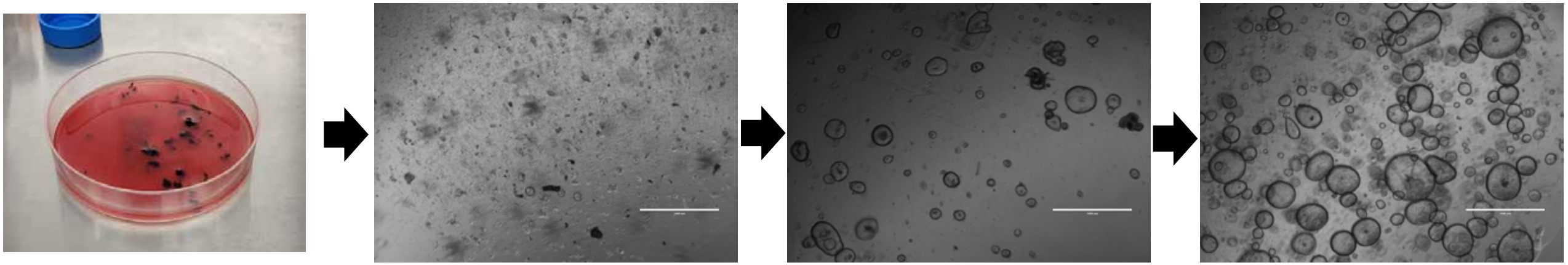
Isolation of Endometrial Epithelial Organoids and Stromal Cells from Menstrual Fluid



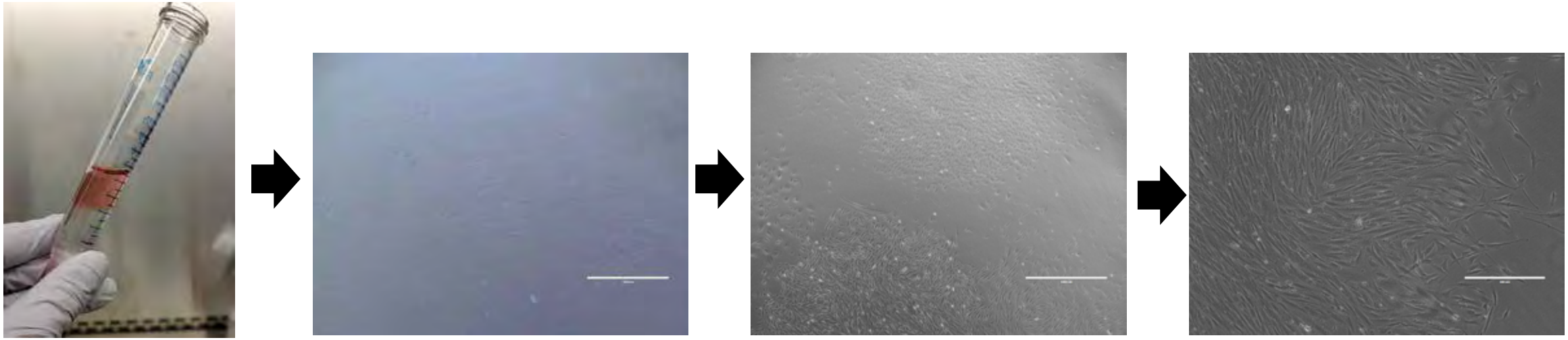
n = 5 per cell type; 4 paired

S. Hewitt & M. Dickson

Organoids from Menstrual Fluid

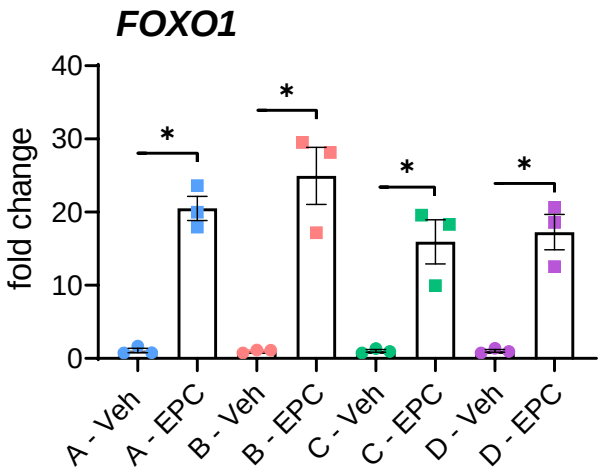


Stromal Cells from Menstrual Fluid



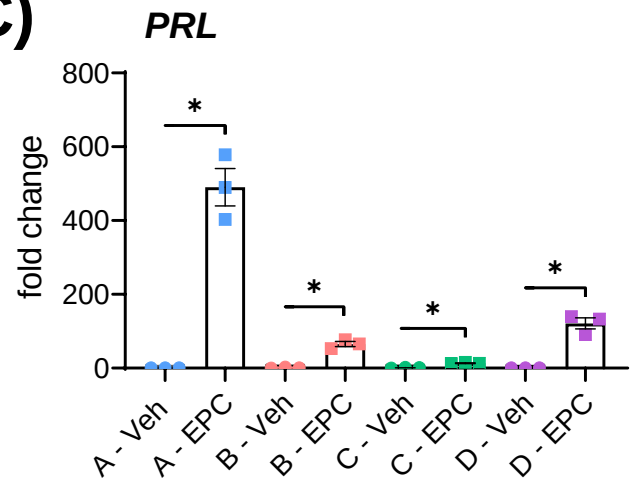
Stromal Cell Decidualization

A)

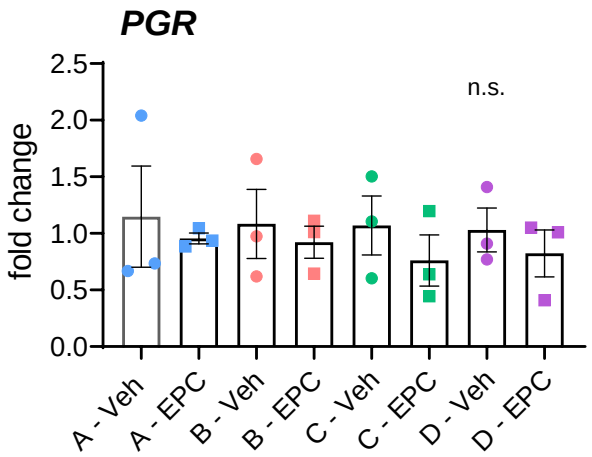


B)

C)



D)



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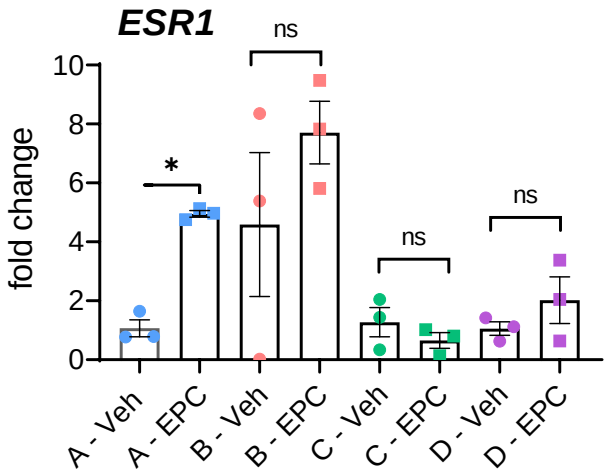
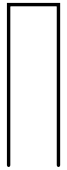


* $P < 0.05$

72 h of EPC

Estrogen Responsiveness

A)



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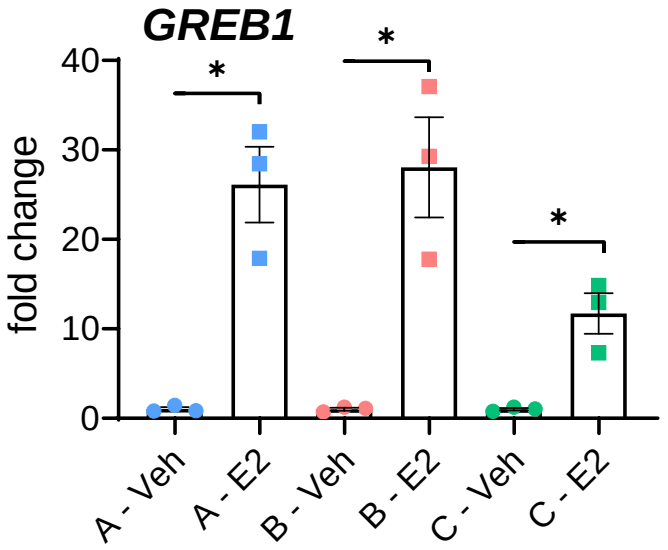

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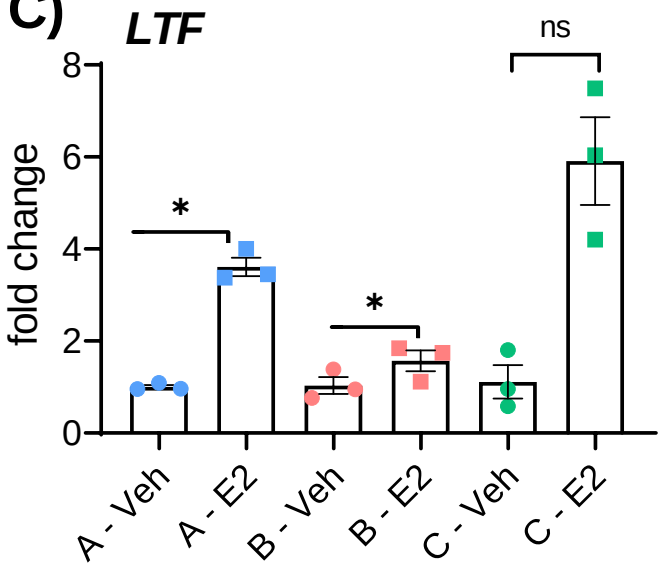
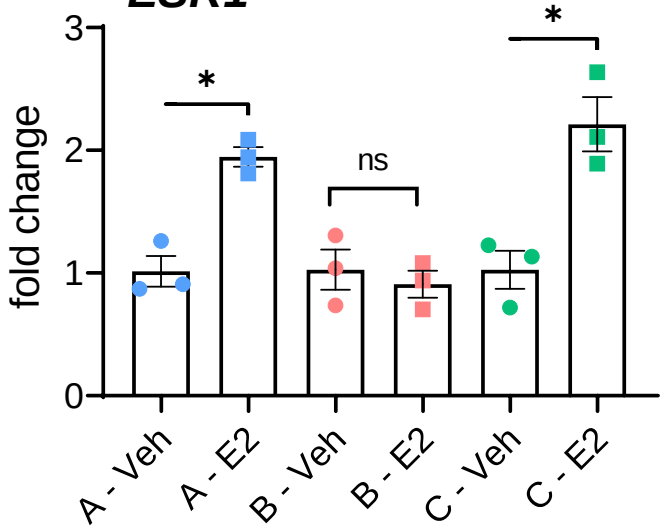


D)



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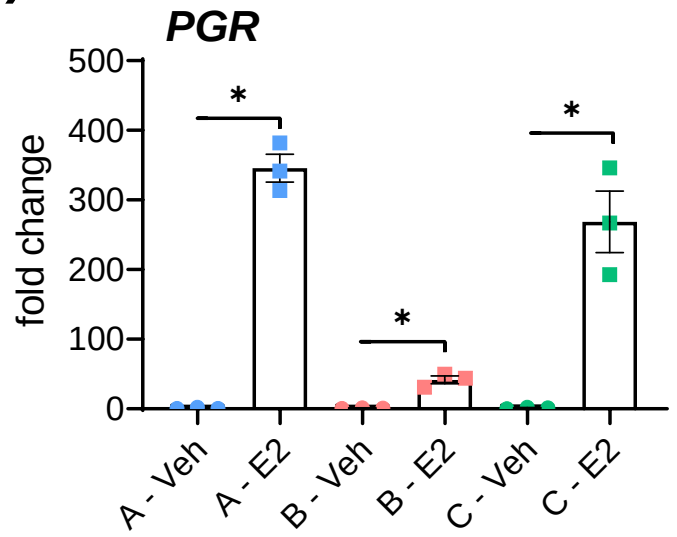
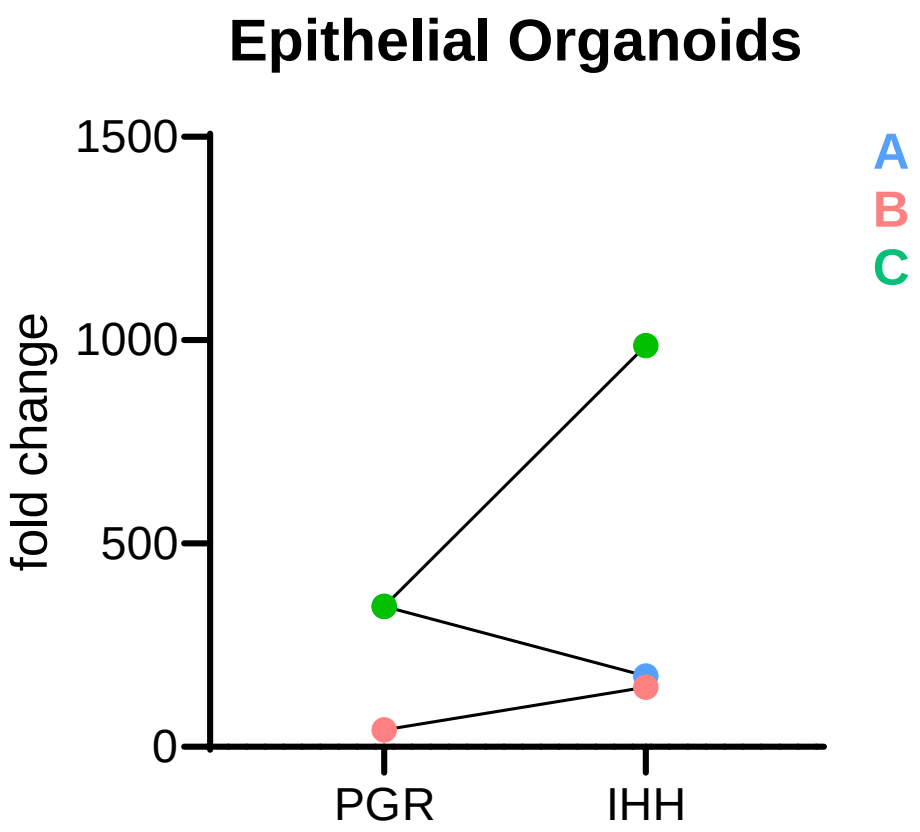
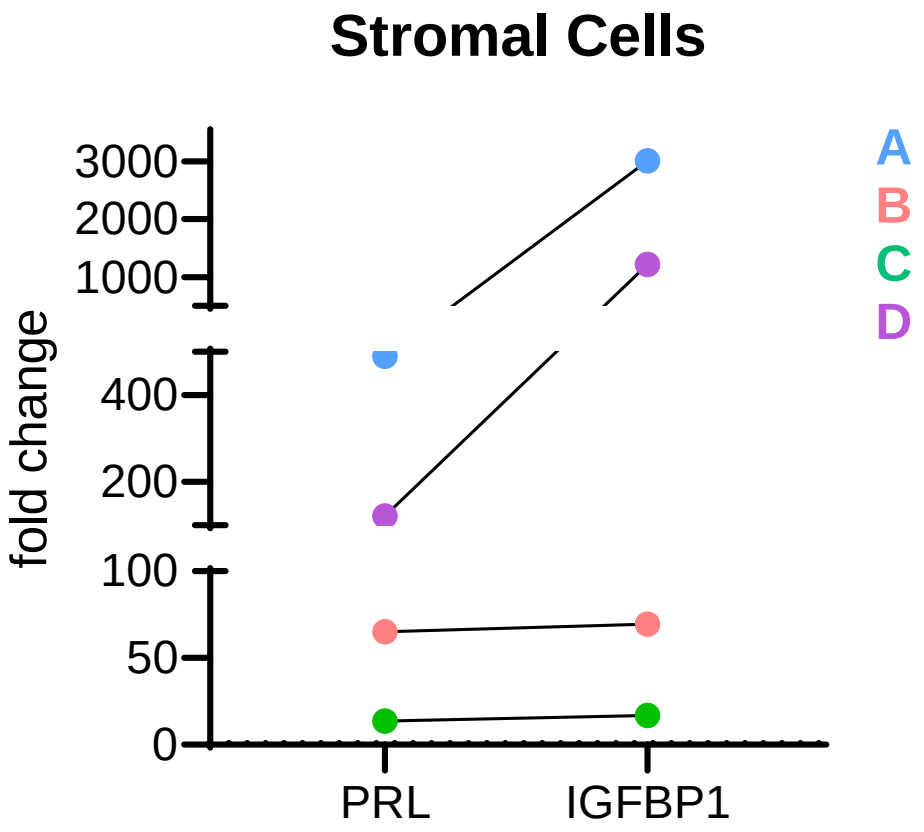


* $P < 0.05$

Relative Responsiveness of Samples from Menstrual Fluid





Advantage of Menstrual Tissue

- Noninvasive means of collecting primary epithelial and stroma cells.
- Can match patient epithelial organoids and stroma in potential coculture experiments
- Can conduct age/environmental effects on epigenome of uterine tissue.

Acknowledgments

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Dr. Francesco DeMayo
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Elvis Quiroz
Frank Orellana
Skylar Montague Redecke

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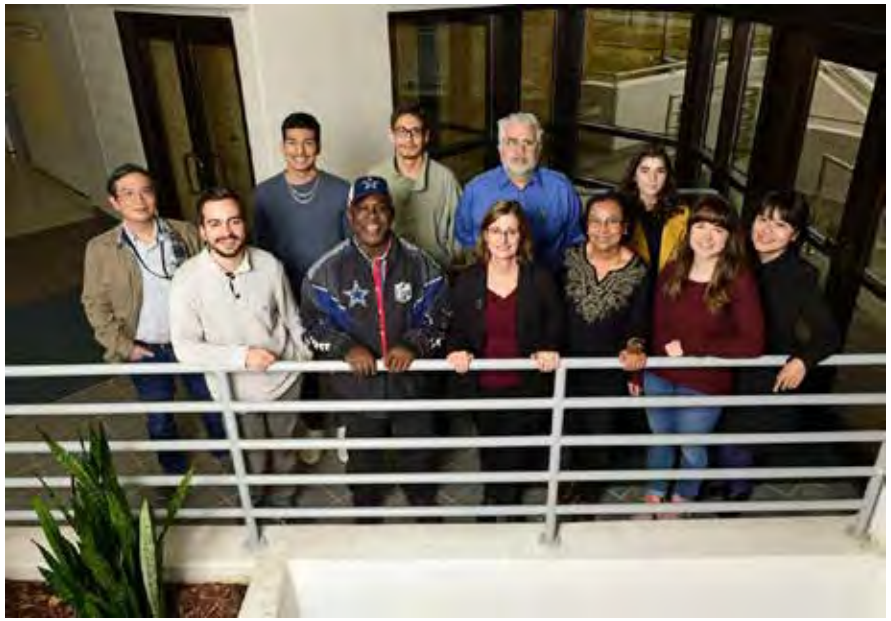
Dr. Wan-Ning ‘Chloe’ Li
Dr. Ru-Pin ‘Alicia’ Chi
Olivia Emery
Yassmin Medina Laver



Epidemiology Branch
Fertility and Reproductive Health Group
Dr. Anne Marie Jukic

Comparative Medicine Branch
Veterinary Medicine Section

Epigenomics and DNA Sequencing Core

Knockout Mouse Core

NIH Research Panel

Carmen Williams, M.D., Ph.D.

Deputy Chief, Reproductive and Developmental Biology Laboratory

National Institute for Environmental Health Sciences

Cellular confusion in the female reproductive tract: A consequence of estrogenic endocrine disruption during development

Carmen J. Williams, MD, PhD

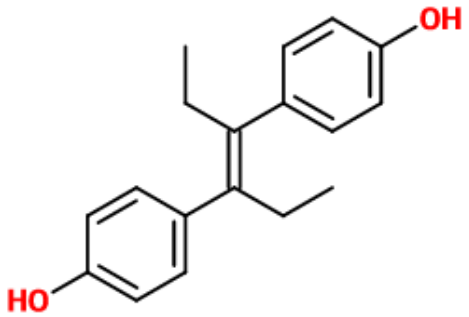
Endocrine Disrupting Chemicals and Women's Health Symposium
July 18-19, 2023

THE ENVIRONMENT INFLUENCES DEVELOPMENT

- Development is genetically and epigenetically programmed
- Environmental cues provide opportunities for adapting development to improve adult fitness
- Altered development can also reduce adult fitness

EXPOSURES DURING HUMAN FETAL DEVELOPMENT CAN AFFECT ADULT HEALTH

- Diethylstilbestrol (DES) is a synthetic estrogen
- Prescribed to 5-10 million pregnant women in the US from 1938-1972; also used internationally
- Heavily advertised to Ob/Gyn physicians

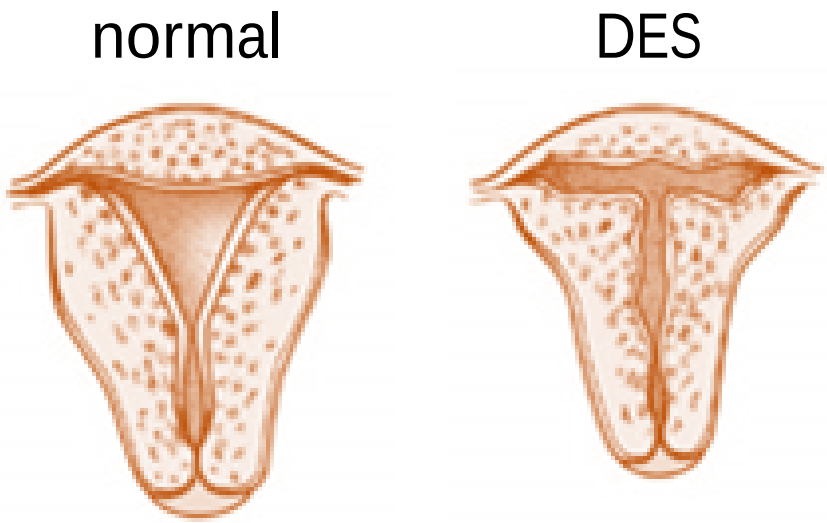


DES

Am J Obstet Gynecol 1957

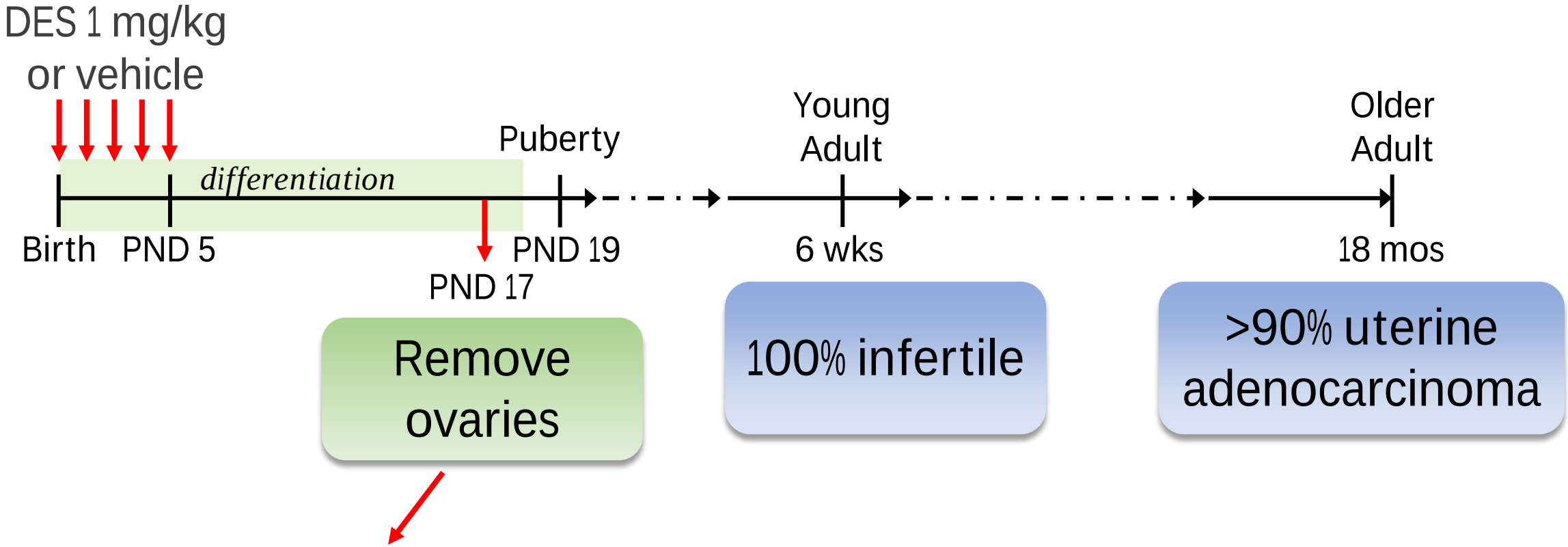
PRENATAL DES ALTERS DEVELOPMENT AND INCREASES CANCER RISK

- Alters developmental patterning of the female reproductive tract
- Causes infertility and pregnancy complications
- Increases the incidence of cancer in adult women
    - Breast cancer
    - Vaginal cancer



MOUSE MODEL OF NEONATAL DES EXPOSURE

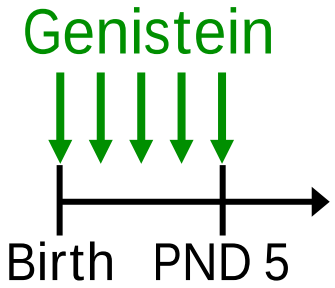
Retha Newbold & John McLachlan

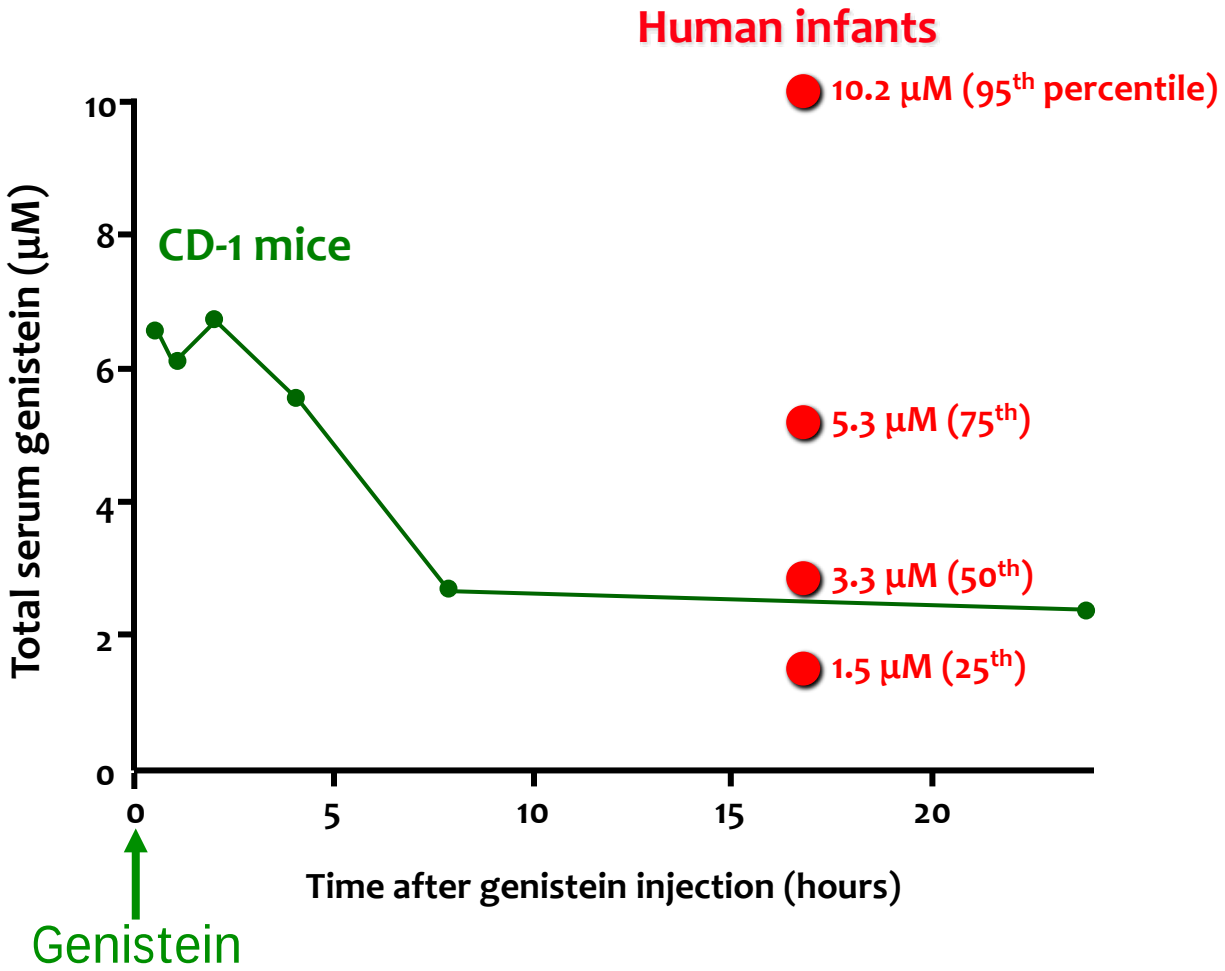


- No cancer develops
- DES-induced cancer requires second 'hit' of estrogen

Newbold et al., Cancer Res (1990)

GENISTEIN DOSING TO MODEL HUMAN INFANT EXPOSURE TO SOY FORMULA

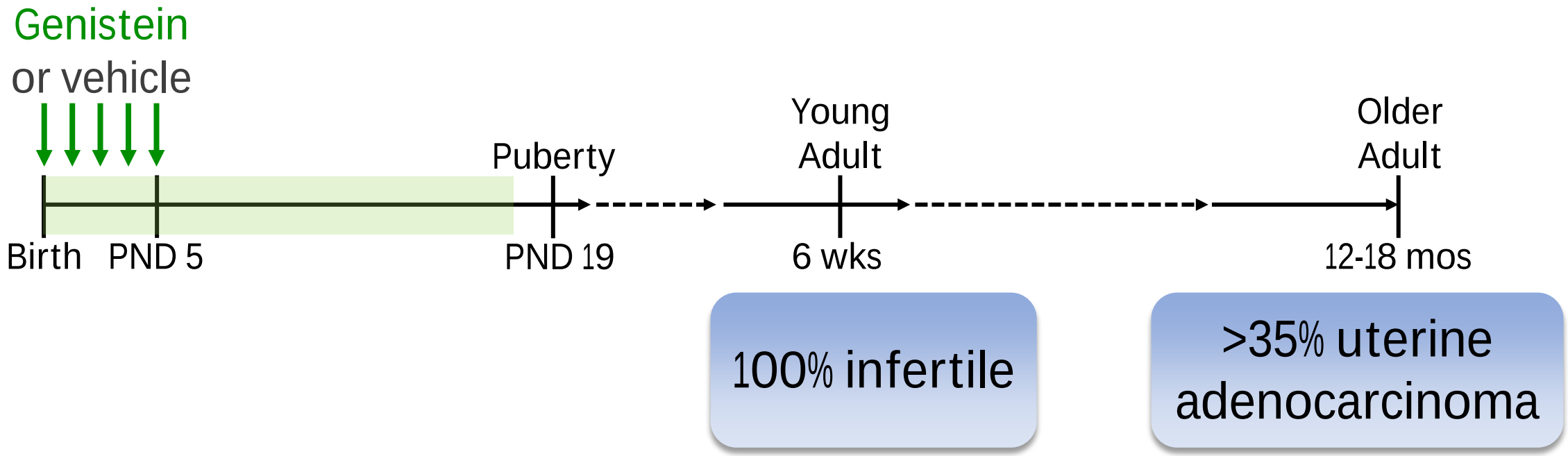




Doerge et al. (2002) Cancer Lett 184:21
Cao et al. (2009) J Expo Sci Environ Epidemiol 19:223

Dosing strategy results in human-relevant serum phytoestrogen levels

EFFECTS OF NEONATAL GENISTEIN EXPOSURE ON FEMALE REPRODUCTIVE FUNCTION

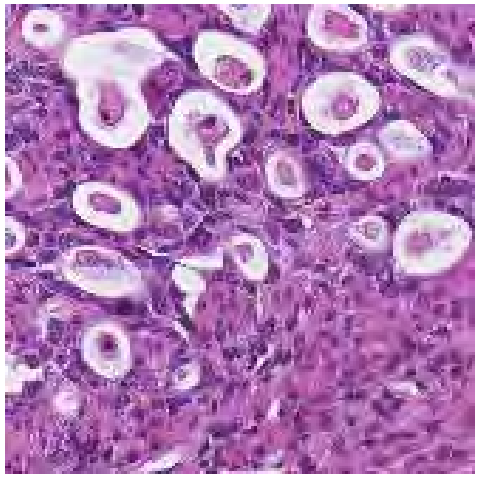


Newbold et al. Cancer Res (2001)

HOW DOES A BRIEF EXPOSURE DURING DEVELOPMENT TO ESTROGENIC CHEMICAL STIMULATION CAUSE ADULT LATE ONSET CANCER?

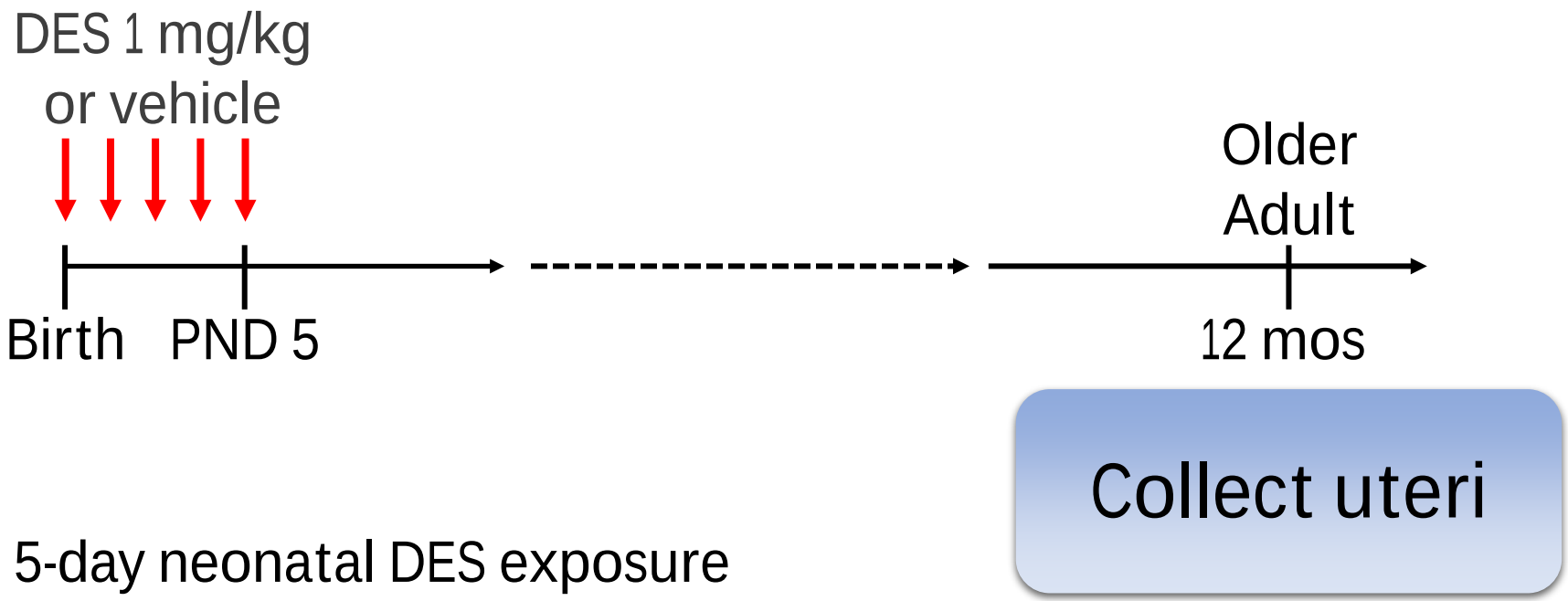
- No mutations in oncogenes or tumor suppressors are found
- There are permanent changes in epigenetic marks, but it is not clear how these changes impact cancer development

Adenocarcinoma



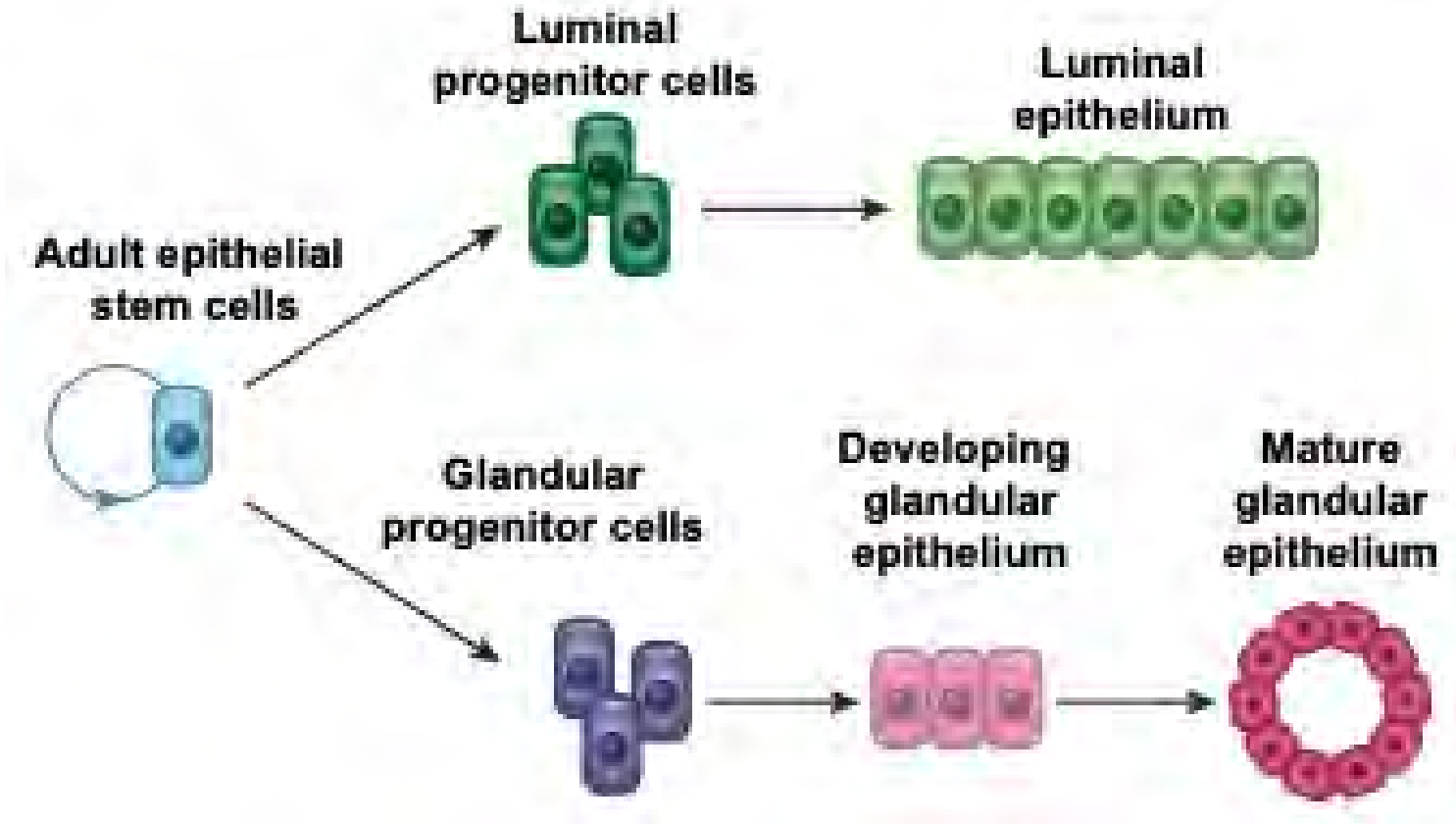
- Experimental approach: Use single cell RNA sequencing to determine how DES exposure alters transcripts in the different uterine cell types, including cancer cells

EXPERIMENTAL DESIGN

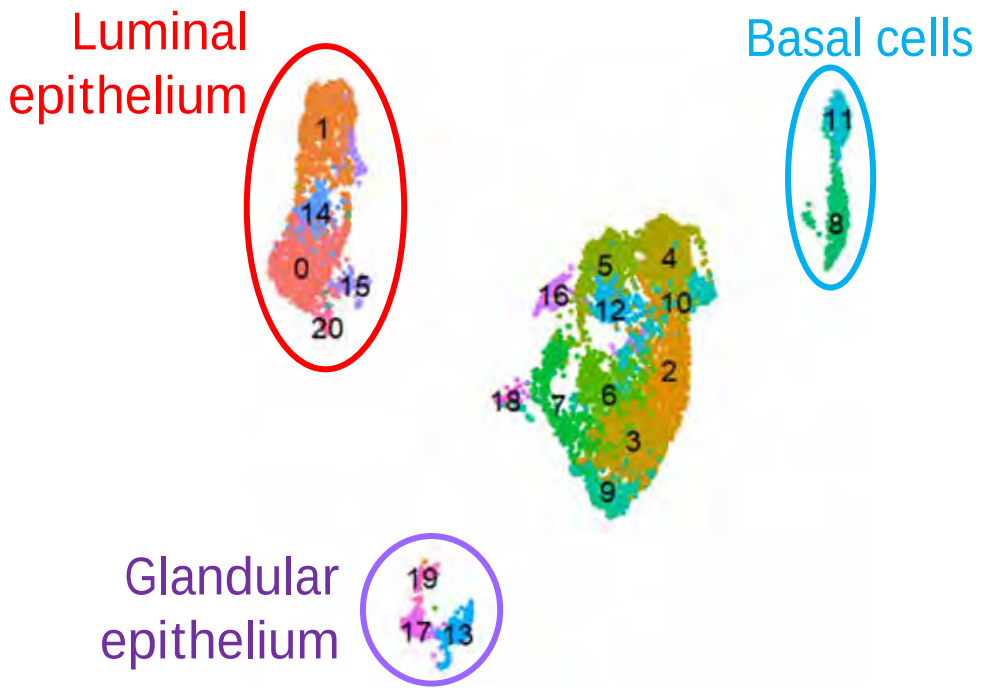


- 5-day neonatal DES exposure
- Collect uteri at 12 months of age
- Isolate living uterine cells for single cell RNAseq analysis

NORMAL UTERINE EPITHELIAL CELL TYPES

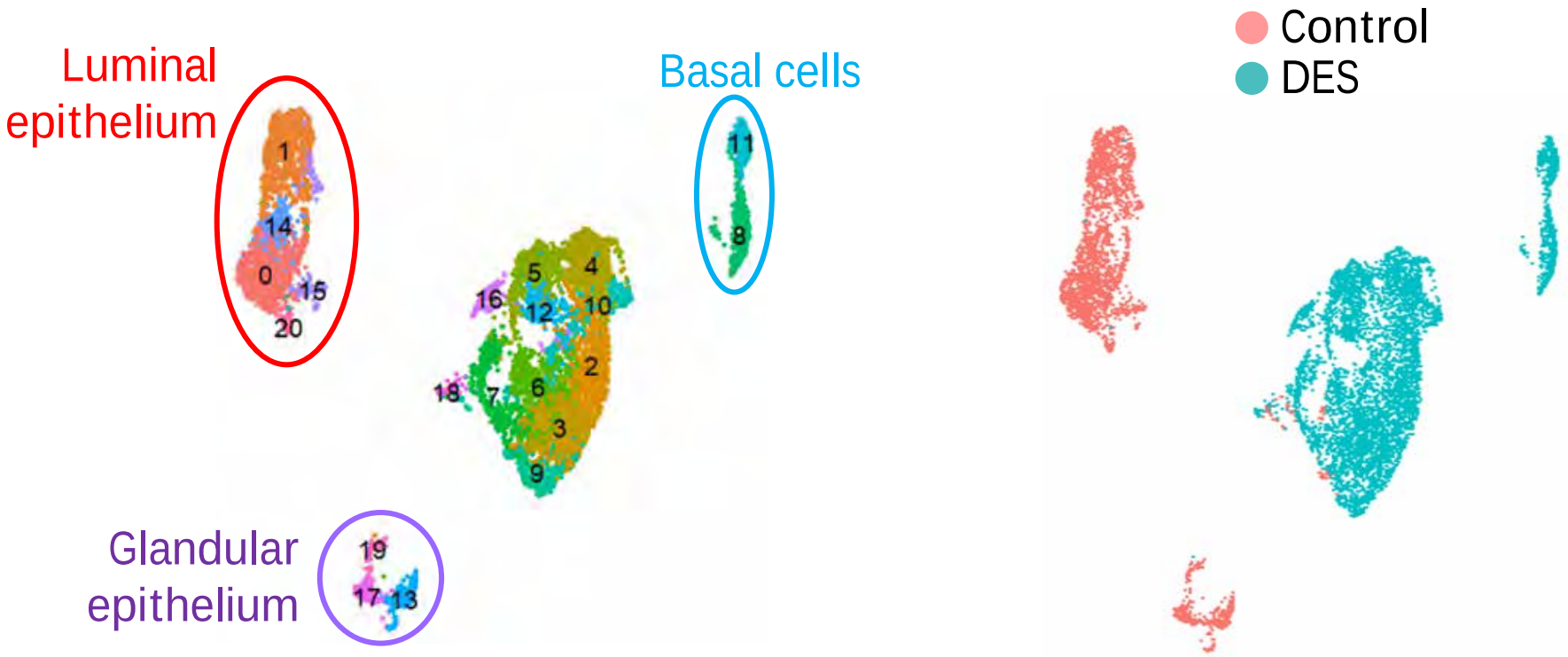


CELL TYPES IN CONTROL AND DES UTERINE EPITHELIAL CELLS



- Luminal epithelium, glandular epithelium, and basal cells were identified using differentially expressed markers
- One large unidentified set of cell clusters was present

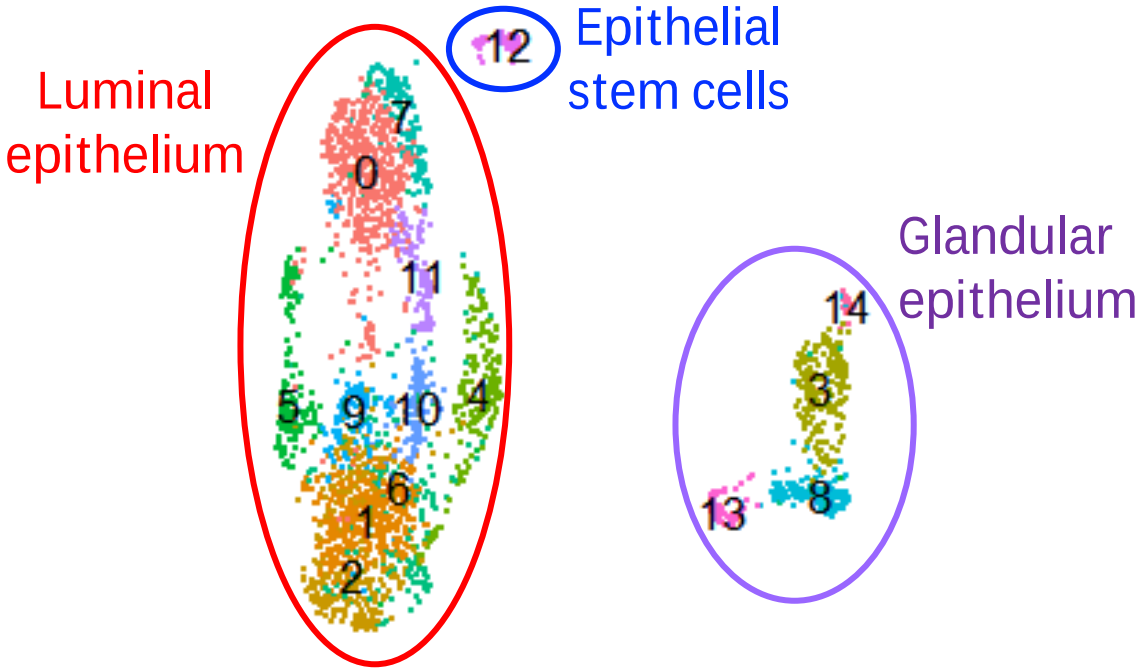
DES-EXPOSED EPITHELIAL CELLS LACK LUMINAL OR GLANDULAR CHARACTERISTICS



- Only CON cells were clearly identifiable as luminal or glandular epithelium
- Basal cells and the uncharacterized large group of clusters almost exclusively derived from DES cells

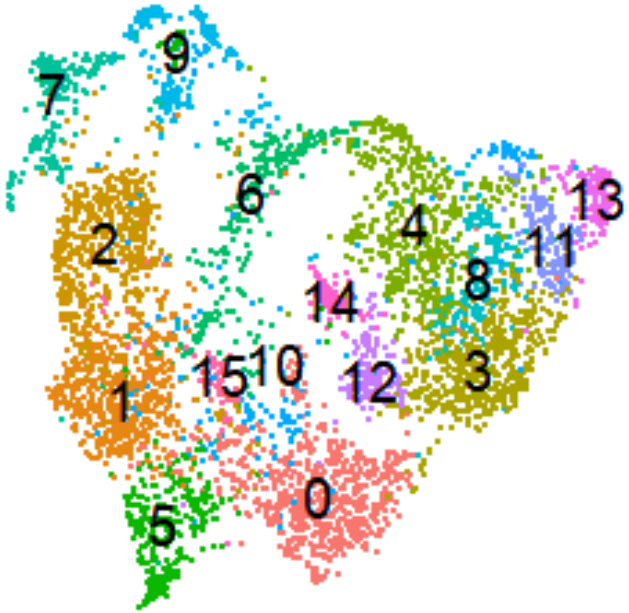
SEPARATE ANALYSIS OF CON AND DES EPITHELIAL CELLS

CON



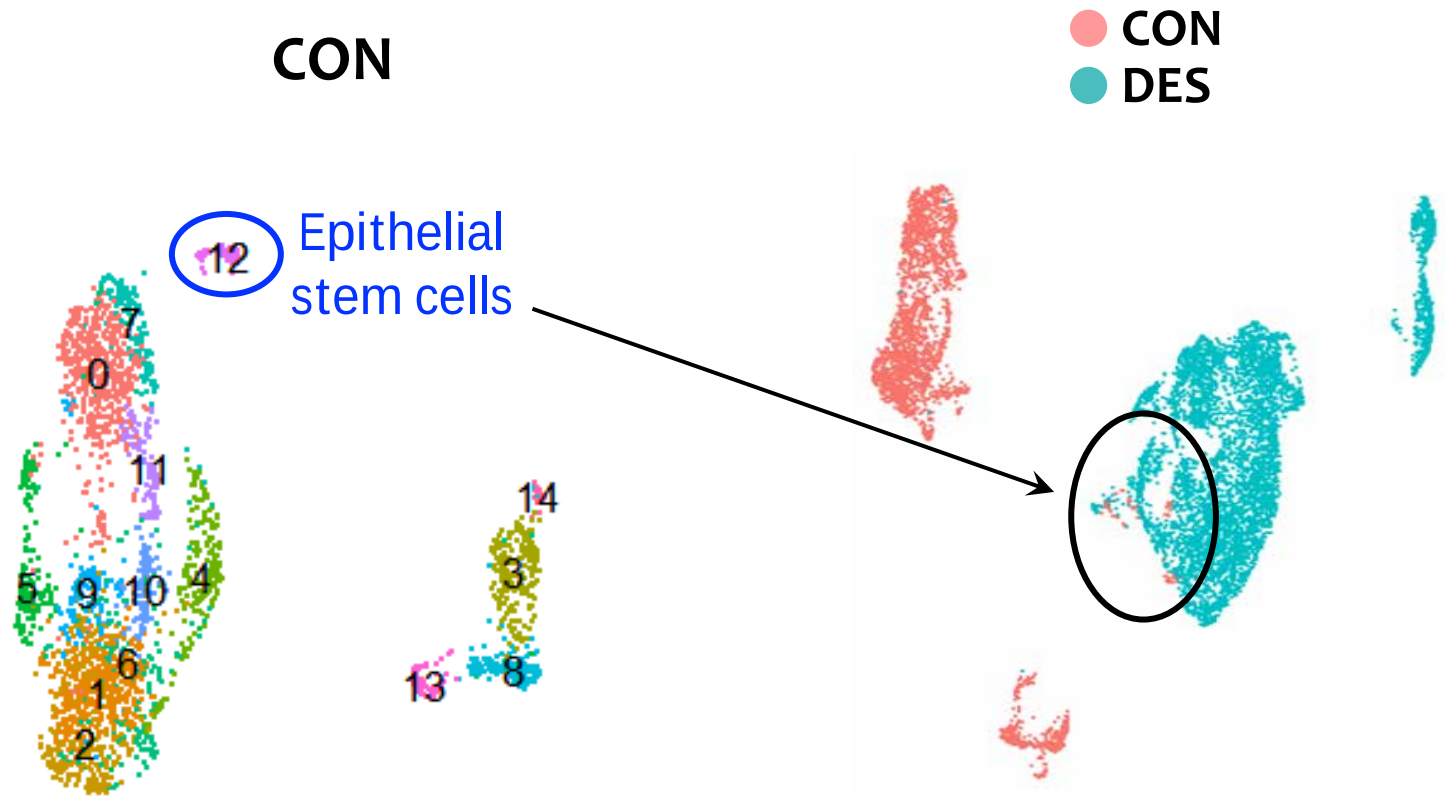
- Three distinct cluster groupings – luminal, glandular, and epithelial stem cells

DES

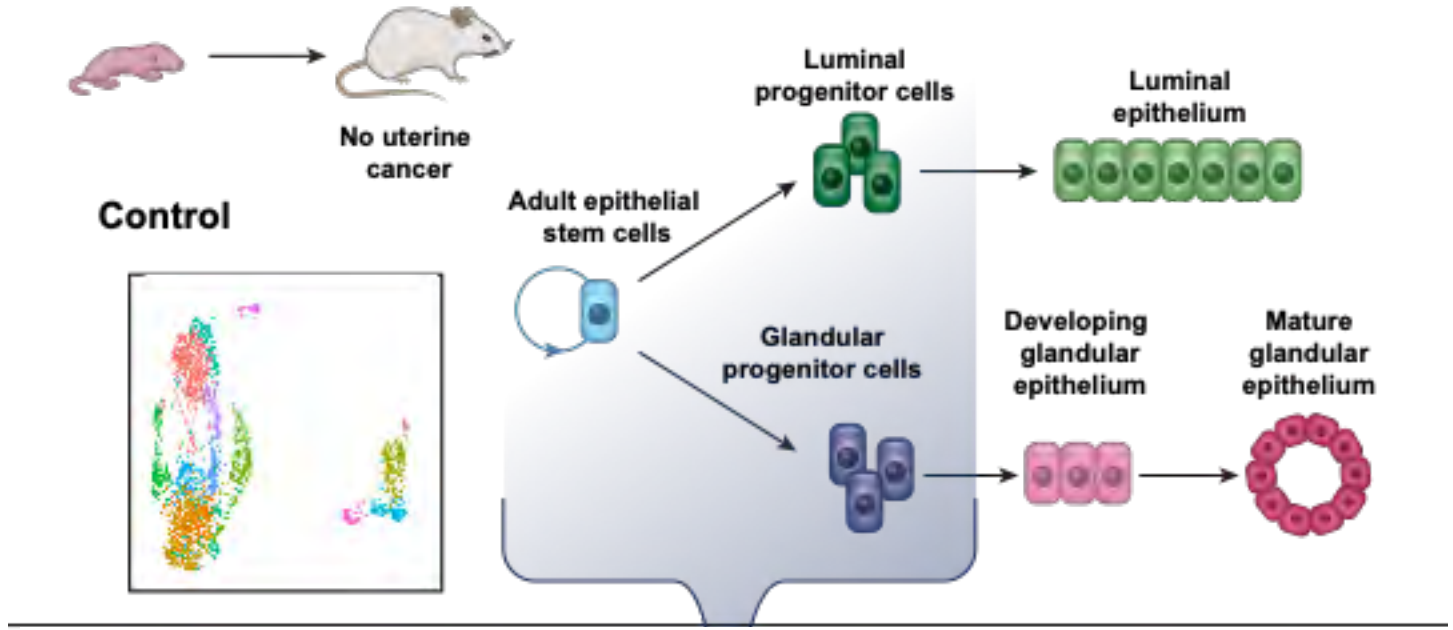


- Basal cells removed from analysis
- One cluster grouping remains – no separation of luminal and glandular cell clusters

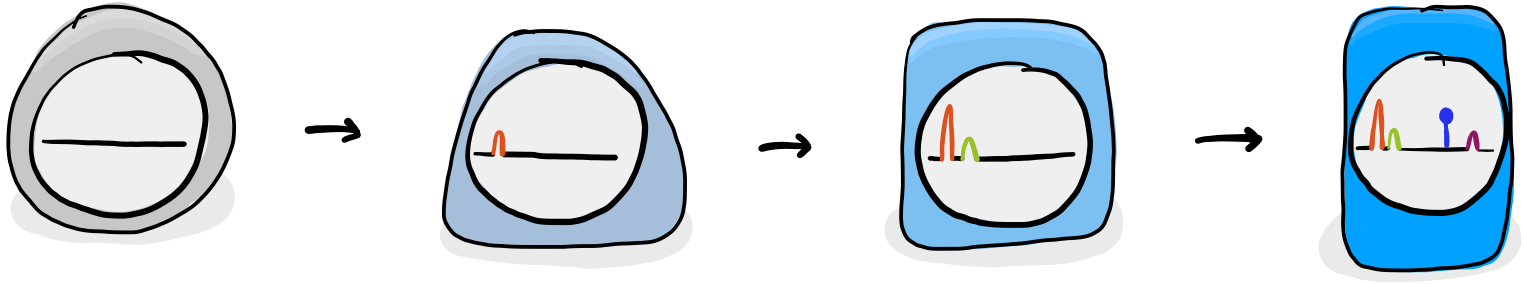
DES EPITHELIAL CELLS HAVE STEM CELL CHARACTERISTICS



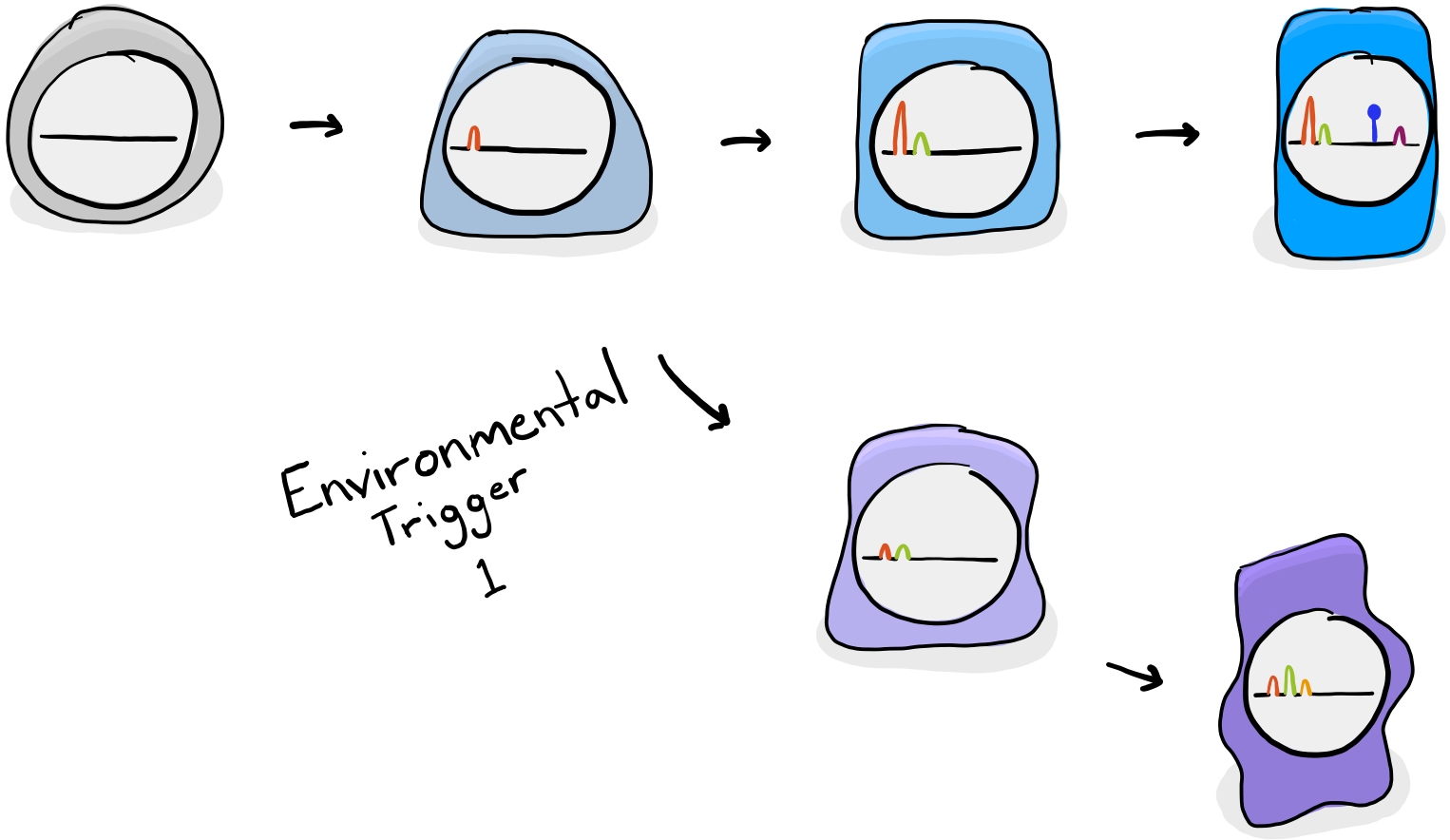
- CON epithelial stem cells cluster with large DES epithelial cell cluster


No uterine cancer
Control
Adult epithelial stem cells
Luminal progenitor cells
Luminal epithelium
Glandular progenitor cells
Developing glandular epithelium
Mature glandular epithelium

CONFUSION OF CELLULAR IDENTITY SENSITIZES CELLS TO ADDITIONAL ENVIRONMENTAL TRIGGERS



CONFUSION OF CELLULAR IDENTITY SENSITIZES CELLS TO ADDITIONAL ENVIRONMENTAL TRIGGERS



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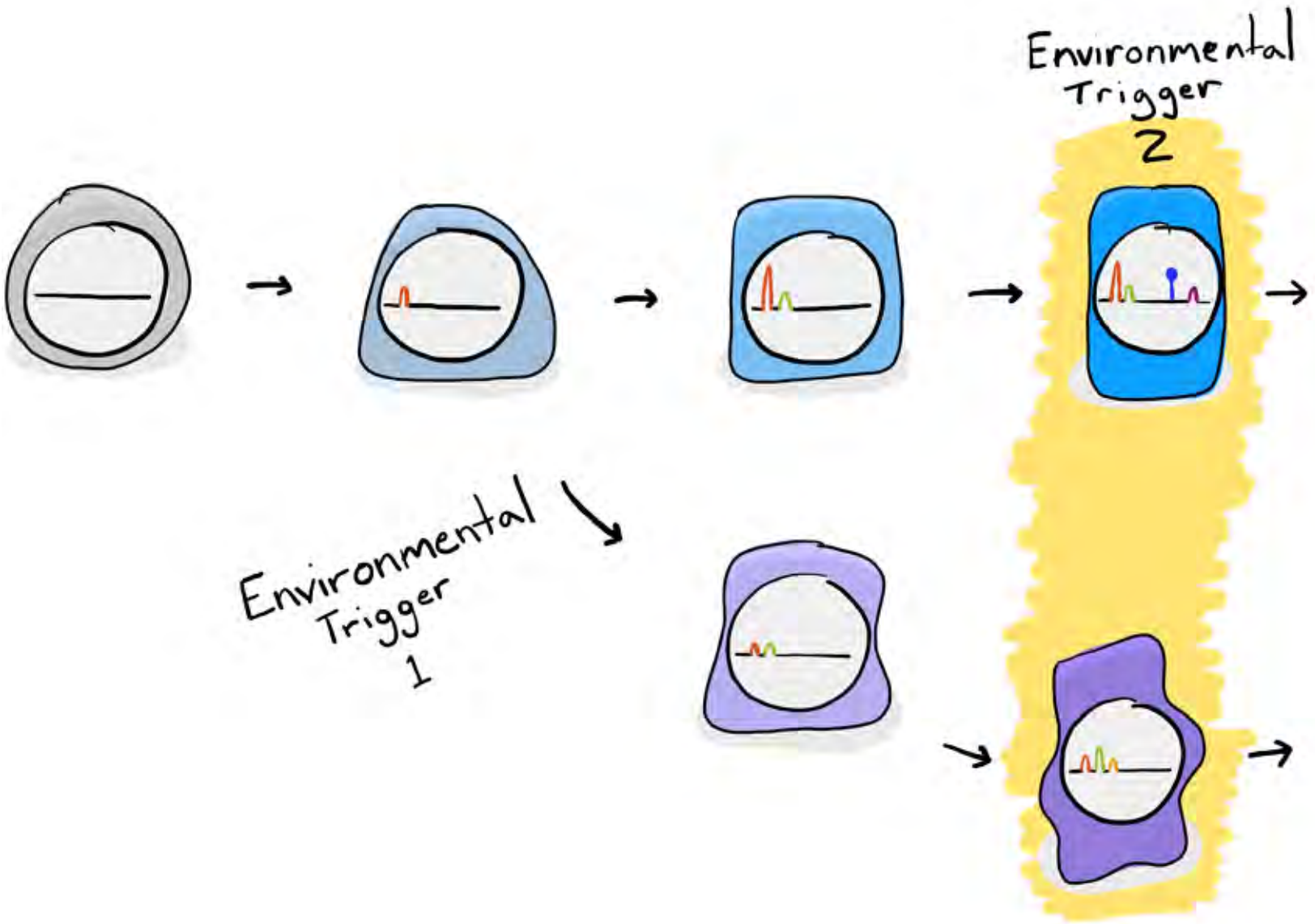

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Williams group

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Lenka Radonova
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Collaborators

Brian Papas (NIEHS)
Xin Xu (NIEHS)

NIEHS Cores

Epigenomics and DNA Sequencing Core
Integrative Bioinformatics Support Group

NIH Research Panel

Janet Hall, M.D., M.S.

Chief, Clinical Research Branch

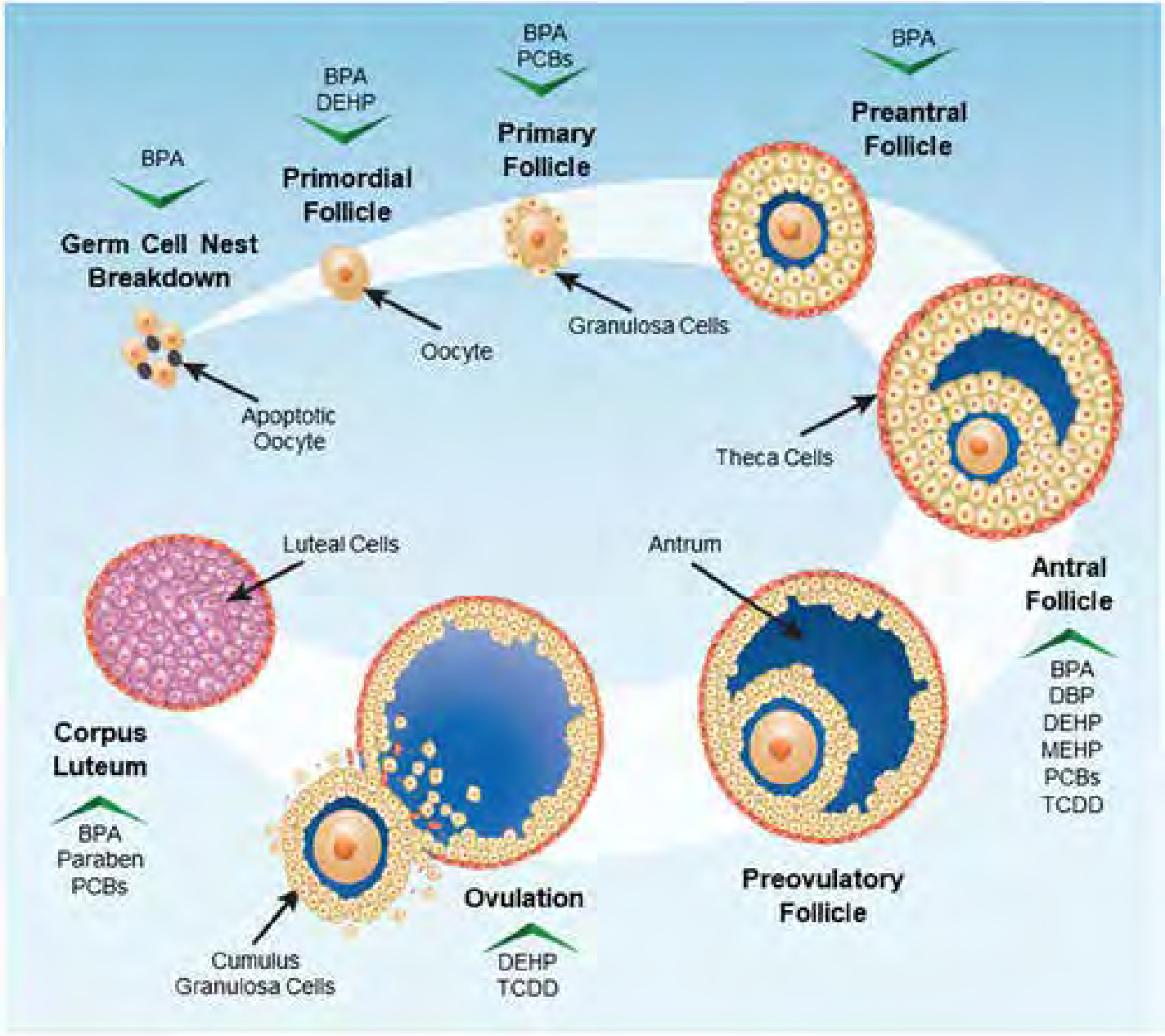
National Institute of Environmental Health Sciences

HHS EDC Symposium
7/17/2023

Does the Environment Affect the Menopause?

Janet E. Hall, MD

Sites of Action of EDCs in the Ovary



The “Bad Actors”

- Persistent Organic Pollutants
- Pesticides
- PFAS
- Phthalates
- BPA
- Metals

Persistent Organic Pollutants and Pesticides

- Highly carcinogenic chemical compounds - electrical equipment like capacitors and transformers, hydraulic fluids
- Banned in the U.S. in 1979 and internationally 2004; still present in pre-1979 products and in landfills
- Forever chemicals that accumulate in food chains, present in soil, air, dust

	Earlier Menopause	POI	Increased FSH	Increased LH	Decreased AMH
Polychlorinated Biphenyls (PCBs)	YES/no	X		X	X
Dioxin	yes/no	X			
Polyaromatic Hydrocarbons (PAHs)		X	X	X	X
Select Pesticides	X	X			

Peri- and Polyfluoroalkyl Substances (PFAS)

- Found in consumer goods such as carpet, leather, apparel, textiles, paper and packaging, coatings, rubber and plastics
- Exposure through contaminated soil, drinking water, food packaging and air
- NHANES – PFAS detected in a high percentage of the population; phase out programs are in effect

Association of PFAS with Earlier Menopause

NHANES 1999-2000 *(Taylor KW, 2014)*

- Women with higher PFAS had earlier age at menopause – consistent across PFOA, PFOS, PFNA, PFHxS
- Could this be reverse causation?

SWAN *(Ding N et al, 2020) (Harlow SD et al, 2021*

- 1,120 mid-life women followed longitudinally to final menstrual period
- Higher PFOS, PFOA associated with shorter time to menopause, particularly in white women;
- Earlier time to menopause associated with an increase in FSH
- PFOA and PFOS were positively associated with FSH; PFOS and PFNA were inversely associated with estradiol
- Prospective design removes concerns of reverse causation

Phthalates

- Used in the manufacture of plastics (increase their flexibility, transparency, durability and longevity), solvents, and personal care products
- Colorless, odorless, oily liquids - do not evaporate easily and do not chemically bind to the material they are added to
- Persist in the environment and have long-term effects through epigenetic effects
- Banned in the EU, Argentina, Japan and other countries; restricted but not completely banned in the US

Association of Phthalates with Earlier Menopause

NHANES 1999-2008 *(Grindler NM et al, 2015)*

- Women with the highest levels of DEHP experienced menopause 3.2-3.8 years earlier than those with low levels

Midlife Women's Health Study 2006-2025

- Baseline analysis from a longitudinal study of 45-54 yo women à 18% increase in odds of recent HF and 38% increase in frequency per doubling of summary measure
- Smaller cohort – high concentrations from use of personal care products à 45% increased odds of experiencing a HF
- Longitudinal analysis found individual metabolites to associate with HF

Association of Phthalates with POI and Poor IVF Outcomes

EARTH Study *(Hauser R et al, 2016)*

- Women undergoing ART (n=256)
- Urinary concentrations of DEHP metabolites were inversely associated with oocyte yield, clinical pregnancy, and live birth following ART

Bisphenol A (BPA)

- Used in food packaging, to line the interiors of food and beverage cans, water pipes, dental fillings
- Repetitive exposure of certain BPA-containing products to light and heat, contact with cleaning agents, and aging of the product may result in increased leaching of BPA into food or beverages
- Human exposure is widespread detected urine, serum, saliva, follicular fluid, breast milk, umbilical cord blood, and amniotic fluid – 93% in NHANES
- A ‘safe’ level has not been established

BPA and Reproductive Aging

Diminished Ovarian Reserve (Cao y et al, 2018)

- BPA levels in the follicular fluid (FF) of patients with diminished ovarian reserve (DOR) were higher than in non-DOR patients while FF AMH and E2 were lower
- FF BPA concentration was inversely correlated with AMH and E2 levels
- Administration of BPA to rodents resulted in decreased AMH and E2

EARTH Study *(Souter I et al, 2015)*

- Prospective cohort of women undergoing infertility treatments
- BPA, detected in >80% of women,
- Average decrease in AFC of 12%, 22% and 17% in the 2nd, 3rd, and 4th BPA quartiles compared to the 1st quartile (p-trend: <0.001)
- No association of BPA with FSH

Metals and Earlier Menopause: Lead

Nurses Health Study *(Mendola P et al, 2014)*

- Bone lead concentration (K-shell X-ray fluorescence) is a marker of cumulative lead exposure (n=434)
- Higher tibial lead concentration was a marker of earlier age at menopause
- Odds ratio for menopause < 43 was 5.3 for women in the highest vs lowest tertile of lead exposure

NHANES 1999-2010 *(Mendola P et al, 2012)*

- U.S. women aged 45-55
- Higher lead levels in menopausal women vs women who were still cycling
- Increased odds of menopause was linearly associated with increasing lead levels (1.7 à 4.2)
  - This relationship persisted even with correction for markers of bone turnover

Endocrine Disrupting Chemicals and Reproductive Aging

Earlier menopause

- ü Persistent Organic Pollutants
- ü Pesticides
- ü PFAS
- ü Phthalates
- q BPA
- ü Metals

Early Reproductive Aging

- ü Persistent Organic Pollutants
- ü Pesticides
- ü PFAS
- ü Phthalates
- ü BPA
- q Metals

You can’t change your Genes…
but you CAN change your Environment!!!

Break

We will resume in Gather.Town at 11:15AM

Virtual Poster Session

Gather.Town

11:15AM – 12:15PM

Join us in Gather.Town for the Virtual Poster Session

How to Join Gather.Town

- Please join our sessions **currently in progress** in Gather.Town
- **The Gather.Town link is available in the chat box as well as on the** website.
- Detailed Gather.Town instructions can also be found on the website.
- Abstracts and posters are viewable on the symposium website and in Gather.Town.
- For assistance, please send a direct message or email to the contracting team:
  - Damon (RLA), damon.kane@roseliassociates.com
  - Sofia (RLA), sofia.jones@roseliassociates.com

Symposium Website

Upcoming Agenda

11:15 – 12:15 PM Virtual Poster Session in Gather.Town

12:15 – 1:00 PM Lunch

Lunch

We will resume at 1PM

Hiding In Plain Sight

Jodi Flaws, Ph.D., Natasha Mesinkovska, Ph.D., M.D.

Moderated by Deb Kilday

Hiding In Plain Sight

Jodi Flaws, Ph.D.

Professor in Comparative Biosciences

University of Illinois Urbana-Champaign

Hiding in Plain Sight (Water Disinfection Byproducts)

JODI A. FLAWS, PH.D.

DEPARTMENT OF COMPARATIVE BIOSCIENCES

UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

Overview

- Background
  - Water disinfection by-products
    - Iodoacetic Acid (IAA)
  - Female reproduction
    - Ovary
- Effects of water disinfection by-products on female reproduction
  - Hypothesis
  - Specific Aims
  - Results
- Summary/Conclusions

Water Disinfection

- A major public health achievement of the last century
- Decreased the incidence of waterborne diseases
  - Cholera
  - Typhoid
  - Amoebic dysentery
- Increased life expectancy

Water Disinfection Byproducts

- The reaction between disinfectants and organic matter form **water disinfection byproducts (DBPs)**

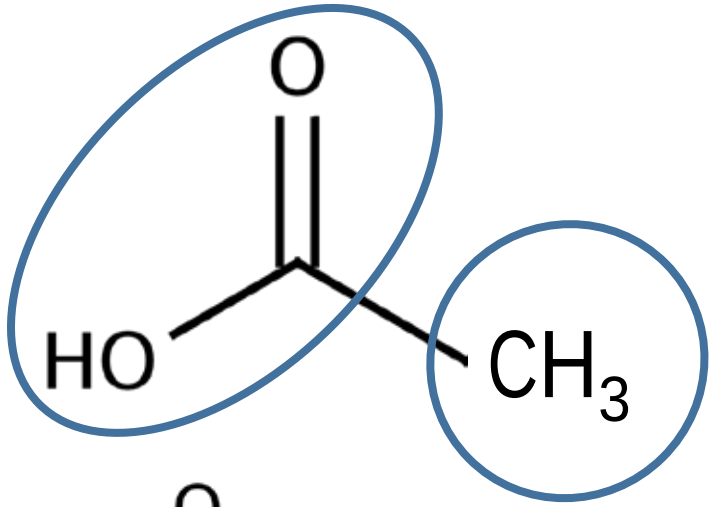
- More than 700 DBPs have been identified in drinking water

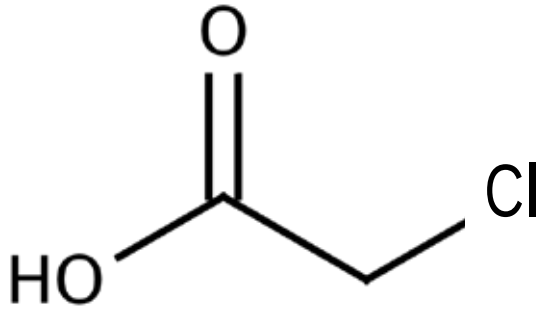
- Trihalomethanes and **haloacetic acids** (HAAs) are the two major classes of DBPs

Haloacetic Acids

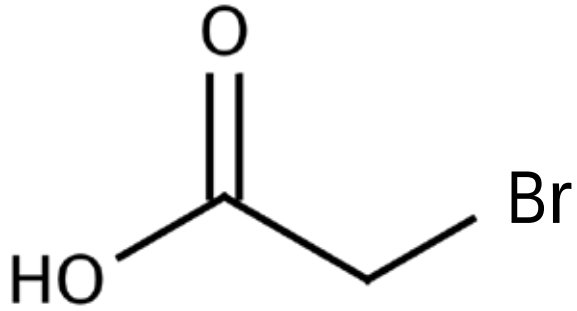
- Haloacetic acids share a common structure with acetic acid

- These molecules consist of two carbons, including carboxylic acid and an alpha carbon

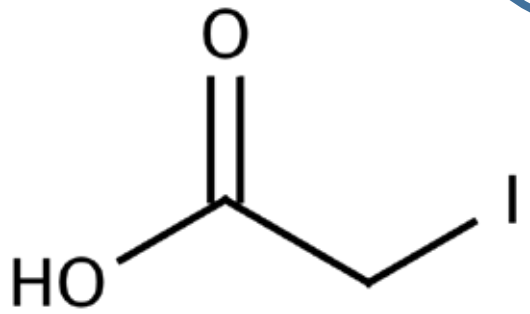




Chloroacetic acid



Bromoacetic acid



Iodoacetic acid

Haloacetic Acid Regulation

- So far, 13 haloacetic acids have been identified in drinking water
- USEPA 1998 - HAA5: chloroacetic acid, bromoacetic acid, dichloroacetic acid, dibromoacetic acid, and trichloroacetic acid

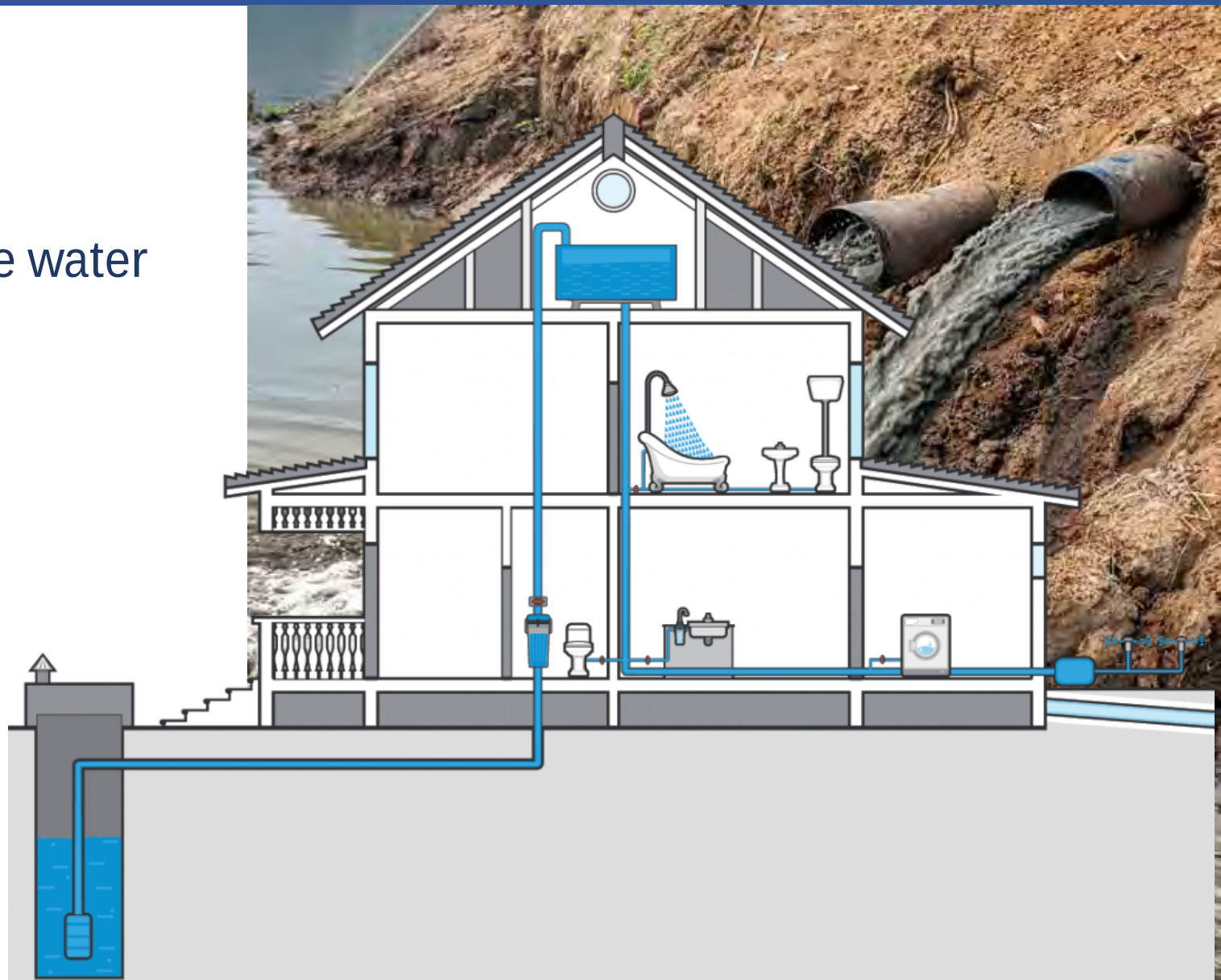
- USEPA 2016 - HAA9: bromochloroacetic acid, bromodichloroacetic acid, chlorodibromoacetic acid, and tribromoacetic acid

Unregulated HAAs?

Iodoacetic acid

Levels of DBPs in Drinking Water are Variable

- Concentration of organic matter
- Chemical composition of the source water
- pH
- Temperature
- Type of the disinfectant
- Concentration of the disinfectant

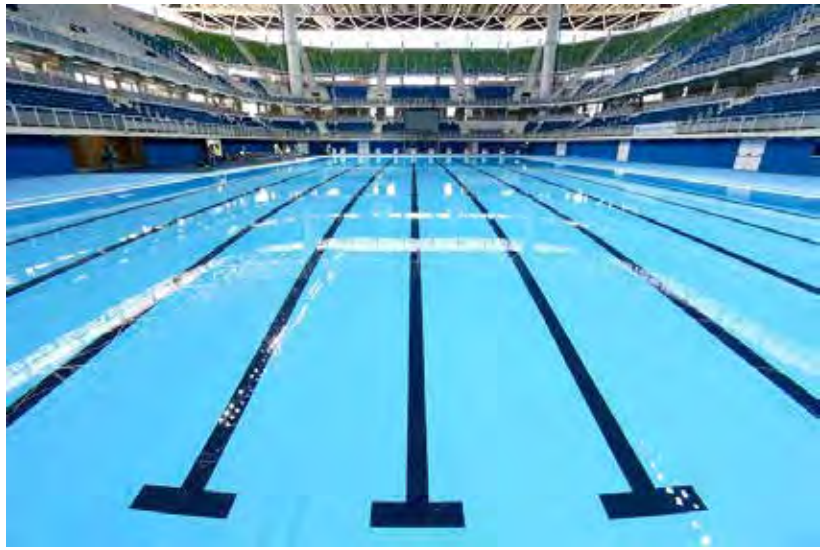


Routes of Exposure

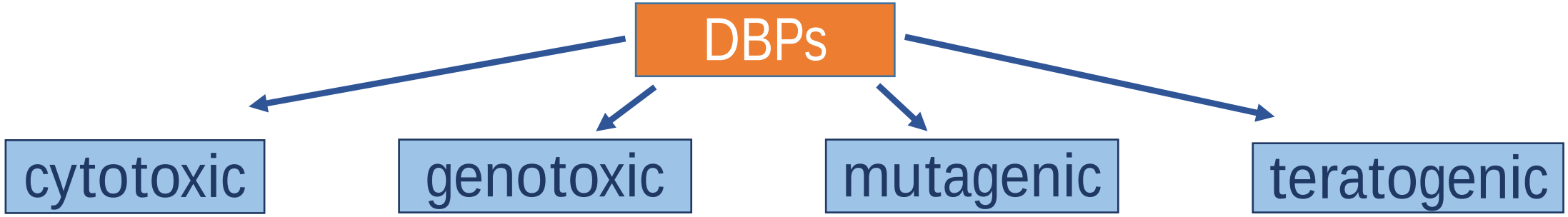
- Ingestion
  - drinking water
  - beverages
  - food

Routes of Exposure

- Inhalation and dermal absorption
  - showers, bathtubs
  - swimming pools, steam rooms



Health Concerns



- HAAs modulate gene expression (Attene-Ramos *et al*., 2010; Muellner *et al*., 2010)
  - stress response to DNA damage
  - cell cycle regulation
  - reactive oxygen species
  - apoptosis

Reproductive Health Concerns

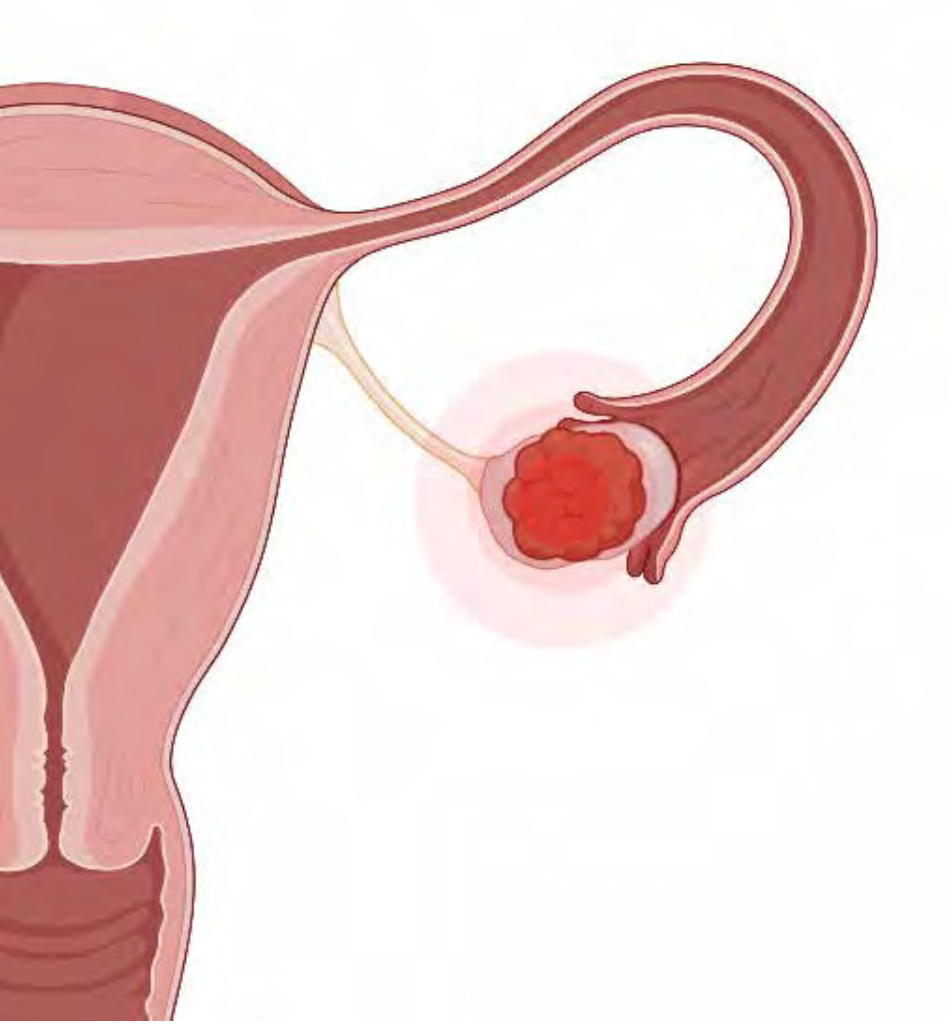
- HAAs disrupt estrous cyclicity and suppress estradiol catabolism, which leads to alterations in steroid production in female rats (Goldmann and Murr, 2003)

- Gestational exposure of a mixture of regulated HAAs results in pregnancy loss and eye malformation in rats (Narotsky *et al*., 2011)

- Adverse pregnancy outcomes (Nieuwenhuijsen *et al.*, 2000; Chisholm *et al.*, 2008; Hwang *et al.*, 2008; Rivera-Nunez *et al*., 2013)
  - low birth weight
  - small-for-gestational age
  - still birth
  - birth defects

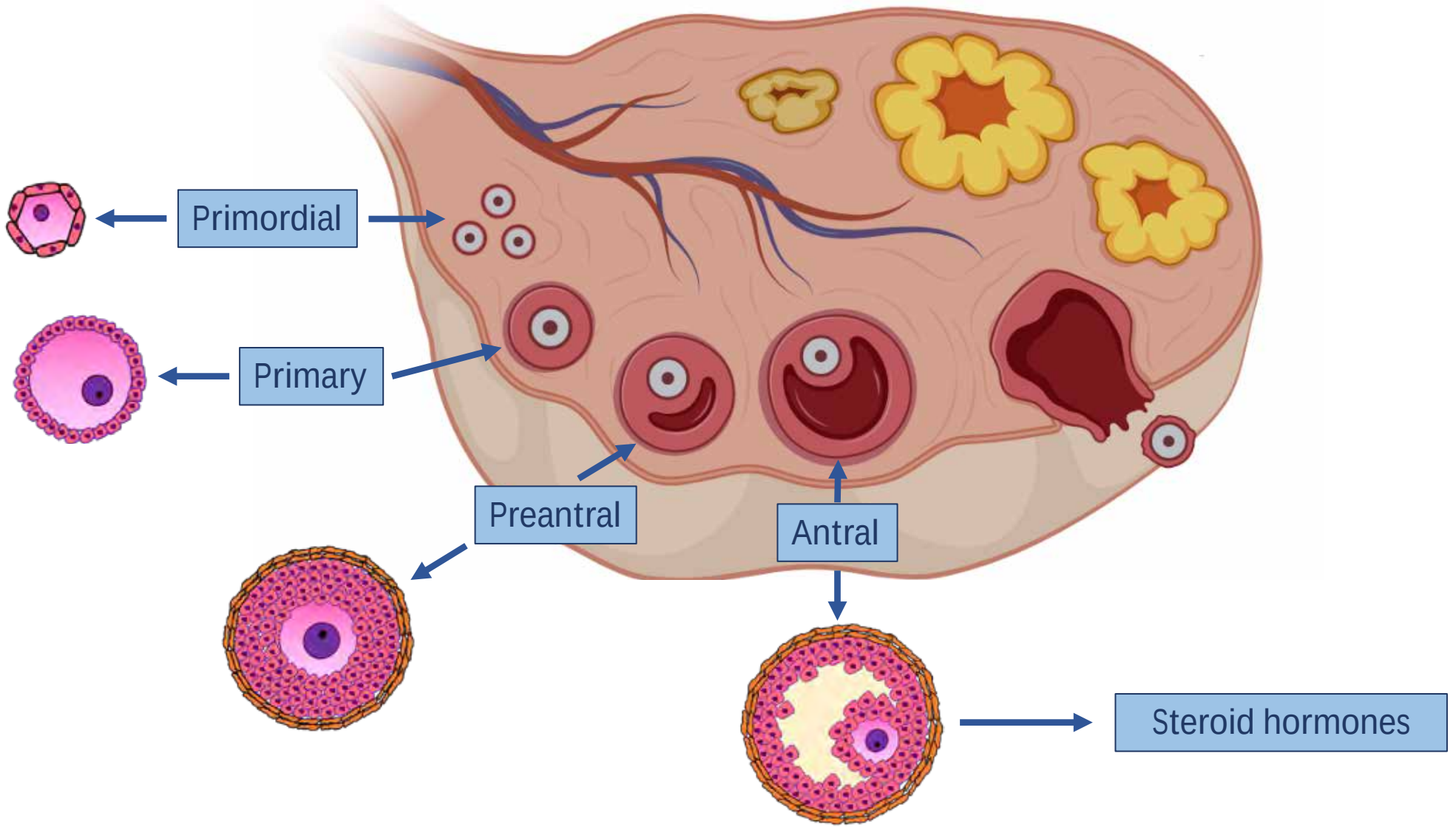
The effects of the HAAs on the ovary are largely unknown

Importance of the Ovaries



- Produce oocytes (folliculogenesis)
  - fertility
- Synthesize/secrete hormones (steroidogenesis)
  - development of eggs
  - estrous cyclicity
  - maintenance of reproductive tract
  - fertility
  - non-reproductive functions
    - cardiovascular, brain, bones

The follicle is the functional unit of the ovary

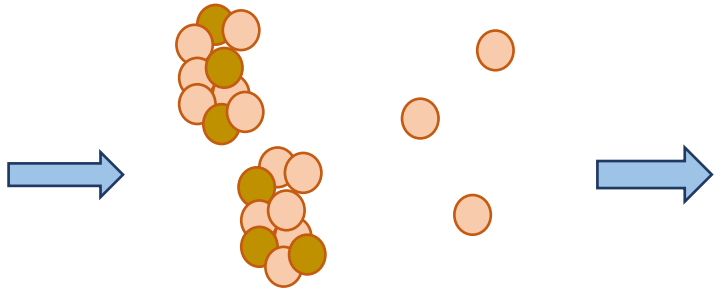


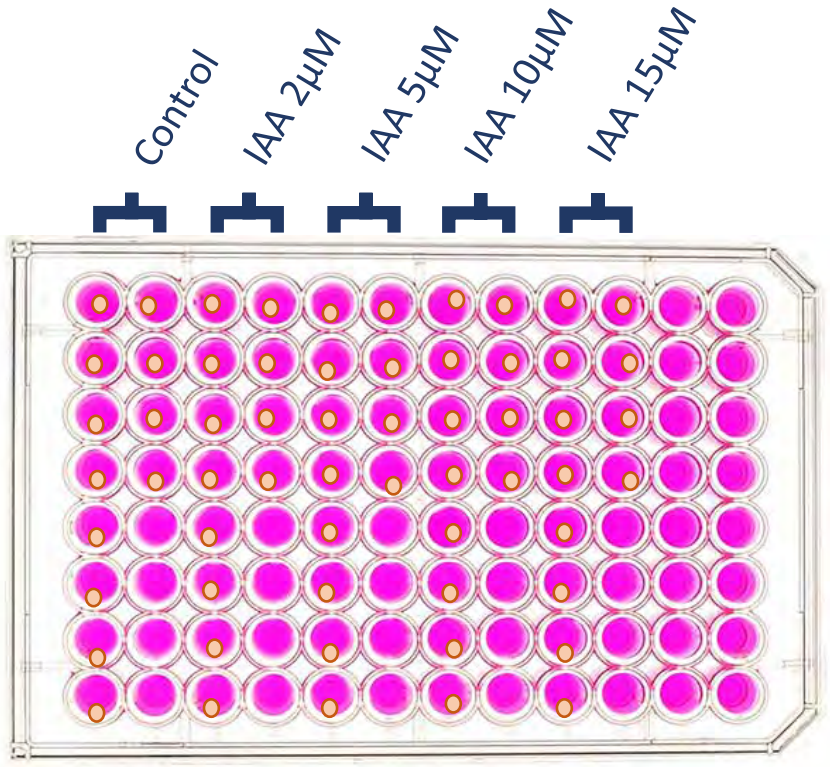
Hypothesis

Iodoacetic acid exposure inhibits antral follicle growth and steroidogenesis

Experimental Design

Follicle isolation



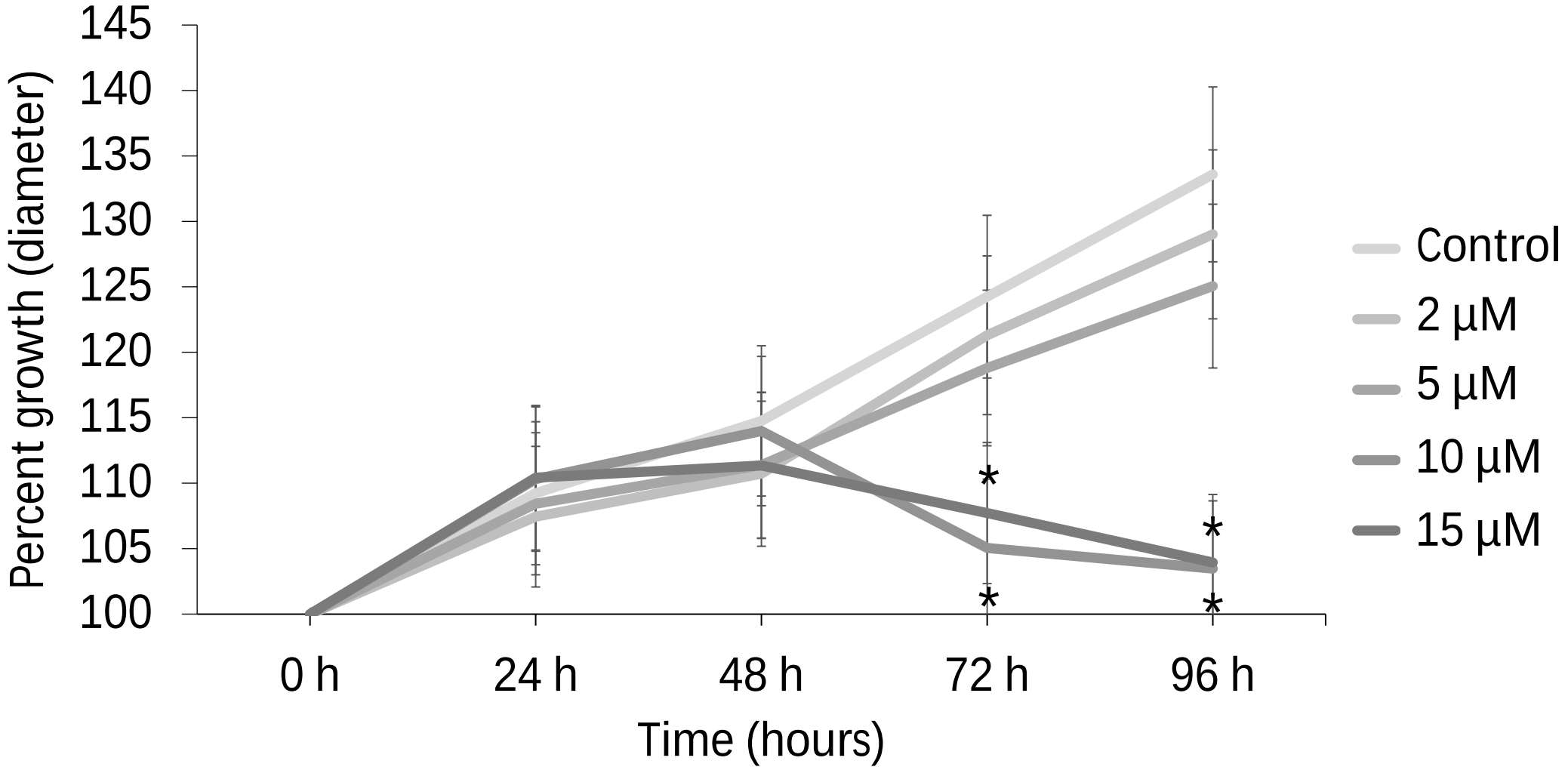


- Ovaries were collected from adult CD-1 mice (32 to 42 days old)

- Antral follicles were dissected from the ovaries and placed individually in 96-well culture plates

- Follicle growth
- Follicular gene expression
- Hormone levels in supernatant

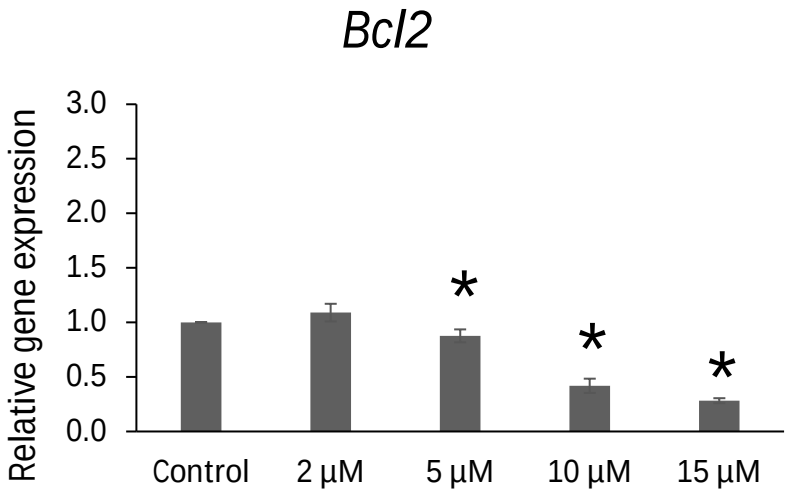
IAA decreases follicle growth in vitro

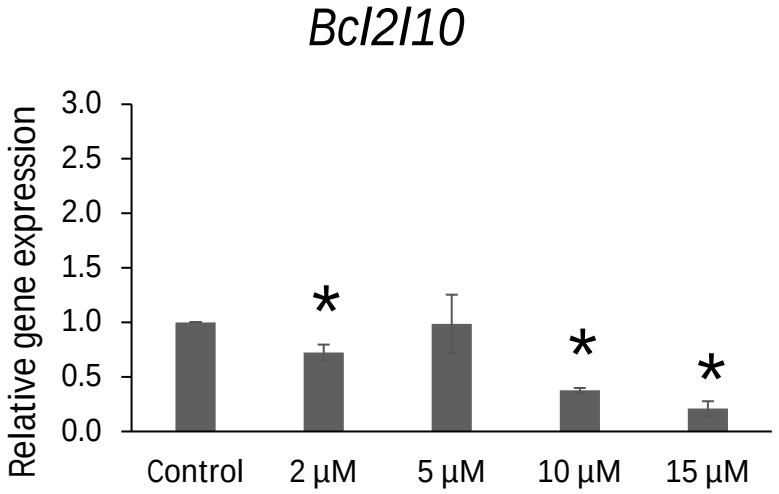


* $p \leq 0.05$

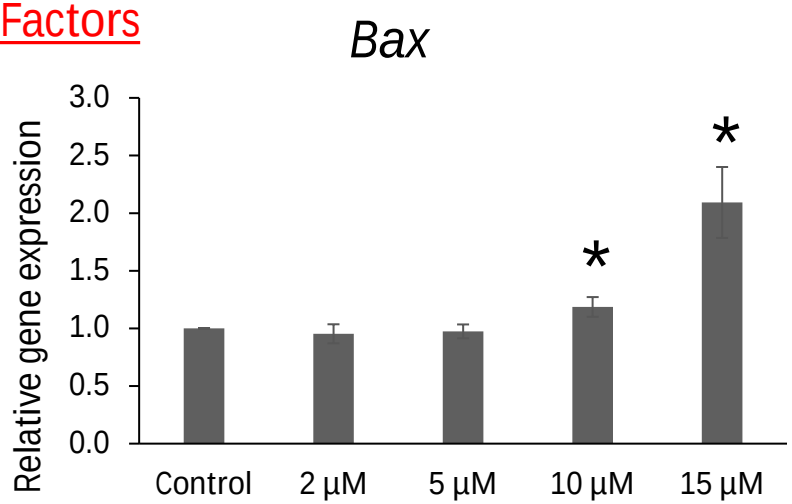
IAA alters expression of apoptotic factors

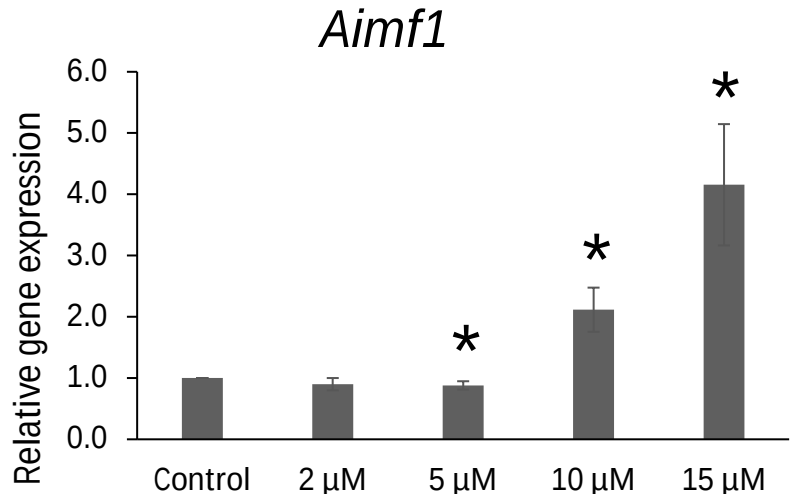
Anti-apoptotic Factors





Pro-apoptotic Factors

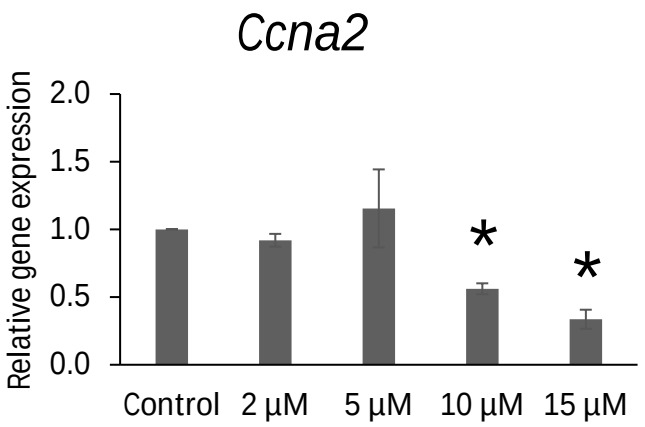


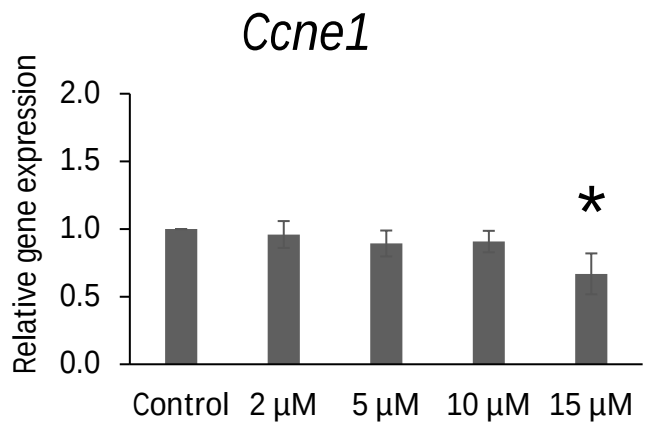


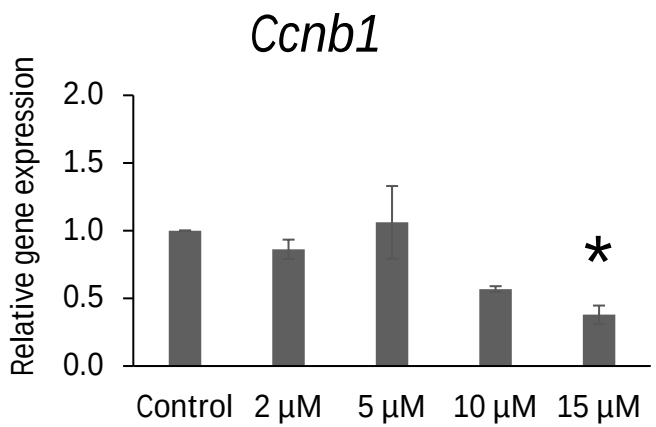
* $p \leq 0.05$

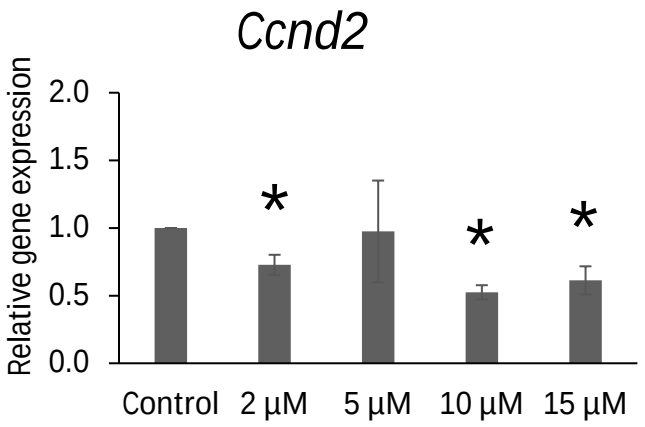
IAA alters expression of cell cycle regulators

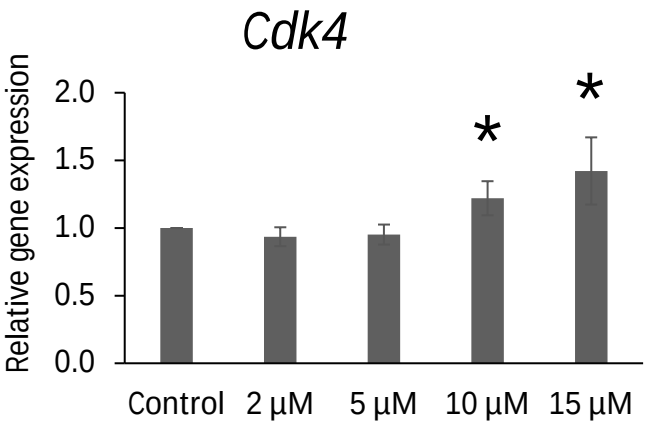
Promoters



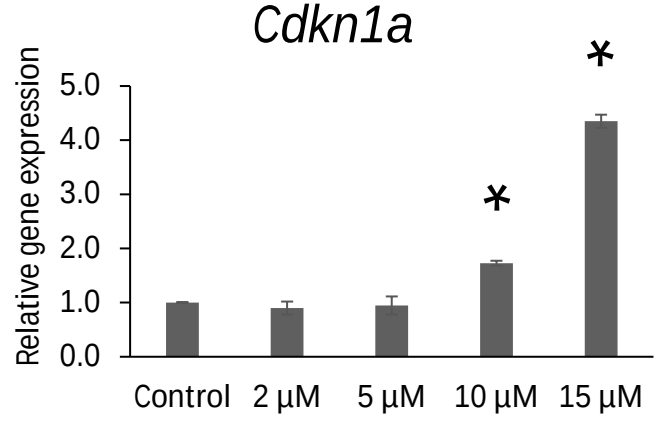






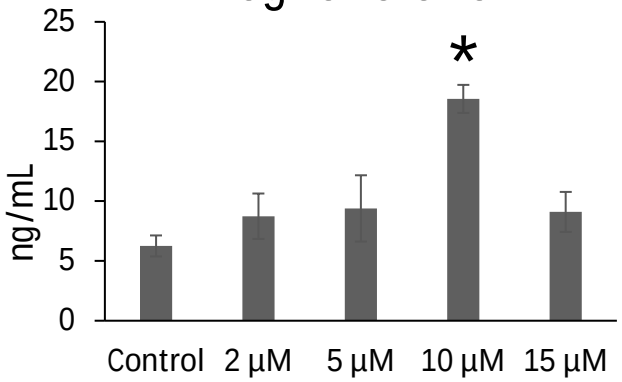


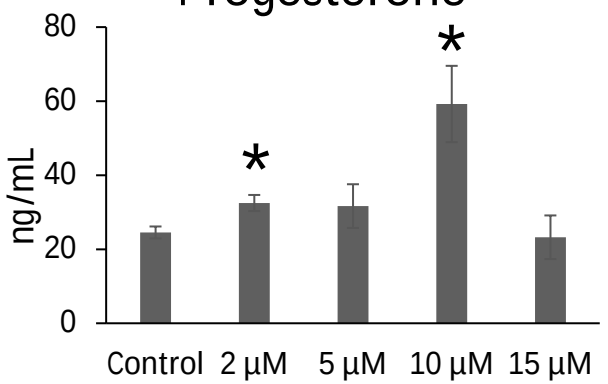
Inhibitor

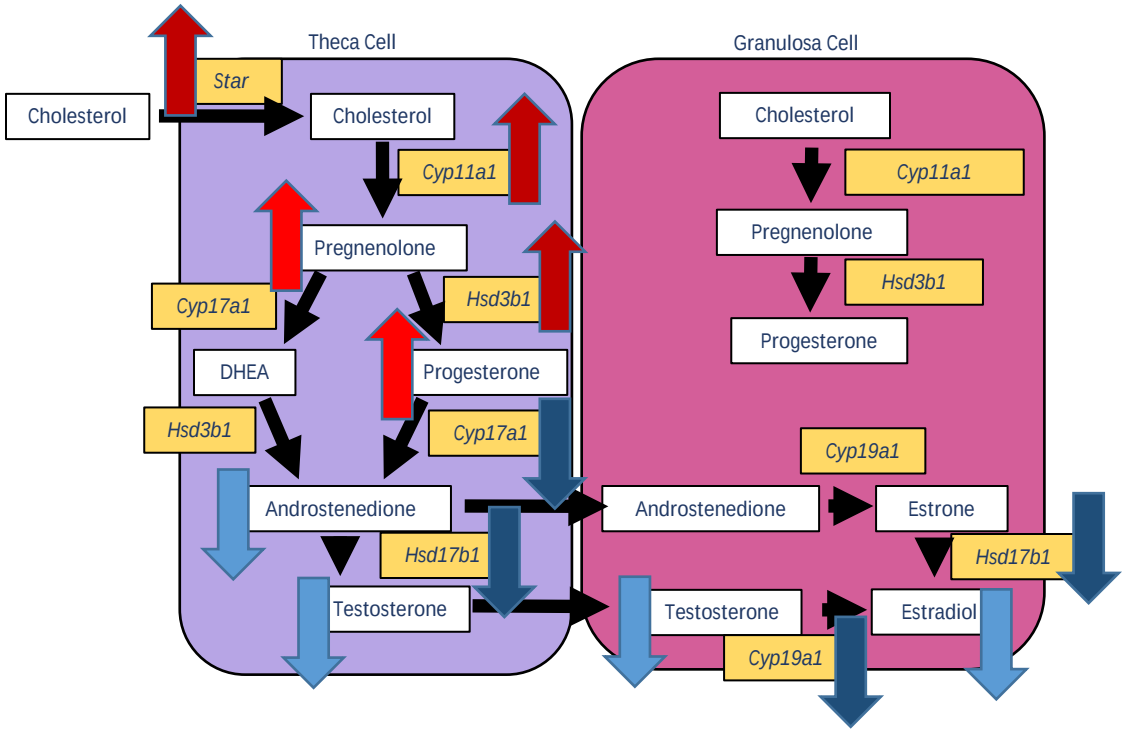


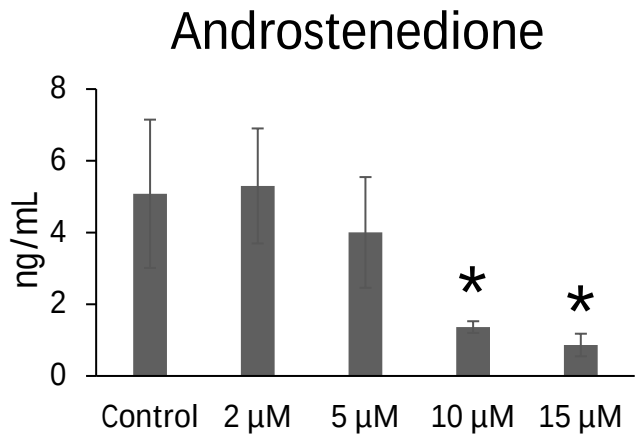
* $p \leq 0.05$

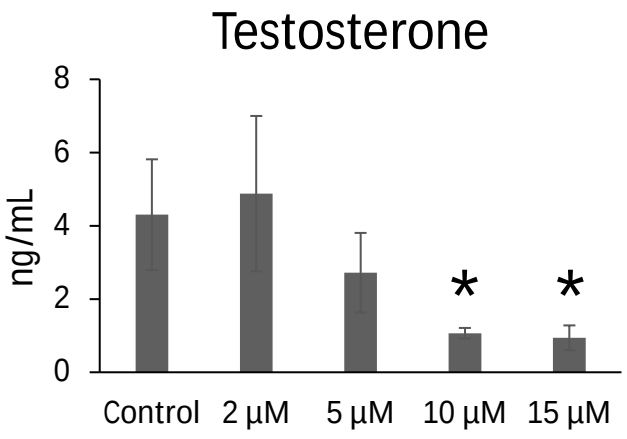
IAA alters sex steroid hormone levels

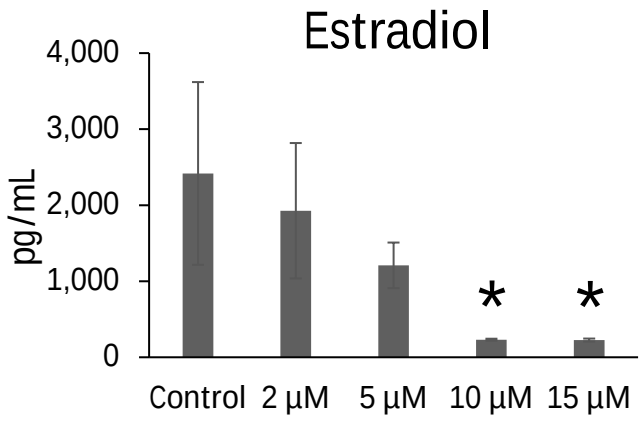






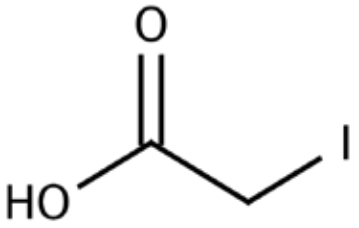






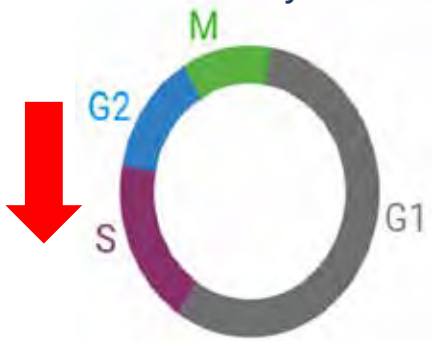
* $p \leq 0.05$

Summary (In Vitro)

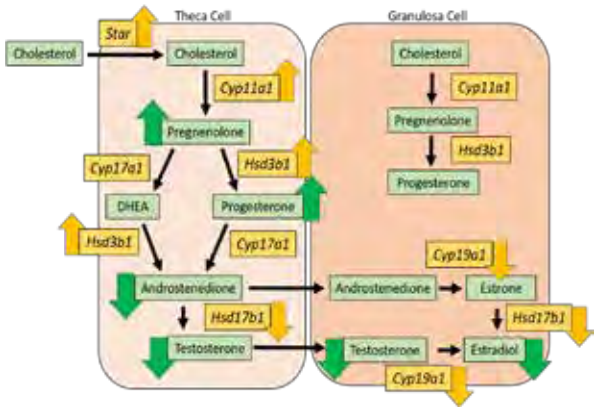


Apoptosis

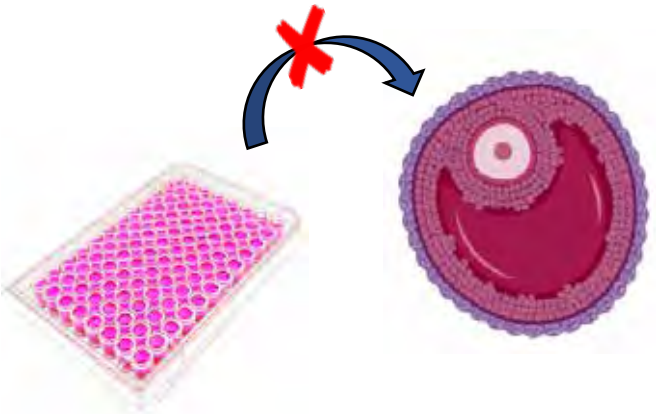
Cell Cycle



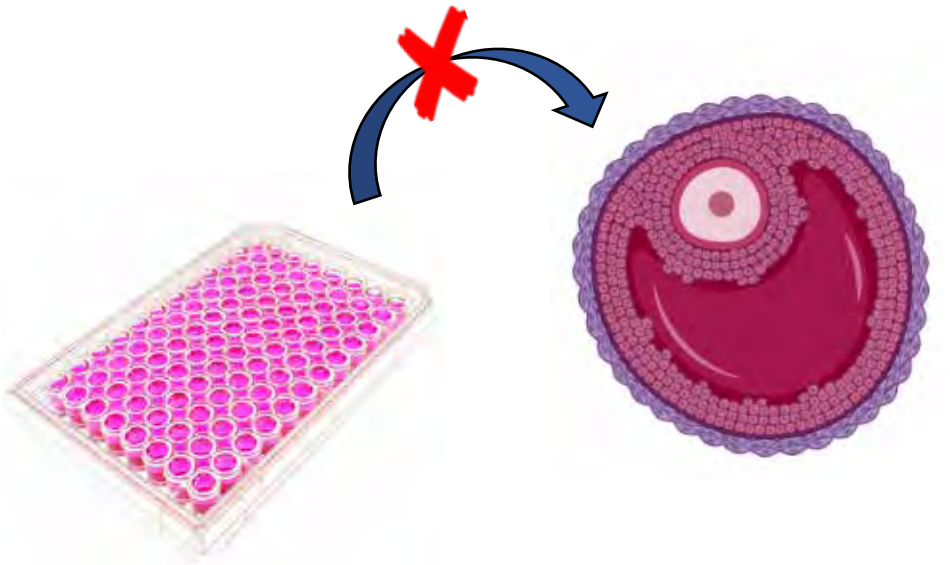
Steroidogenesis



Follicle growth



What about in vivo?



vs.

Hypothesis

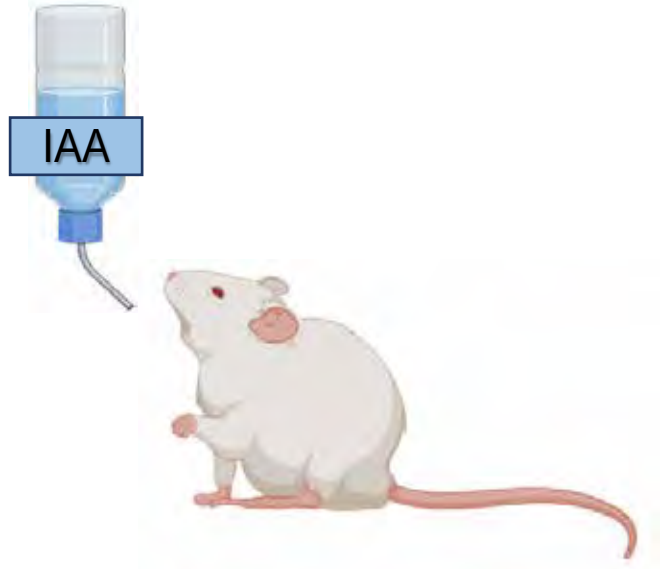
Iodoacetic acid exposure affects female reproductive outcomes in vivo

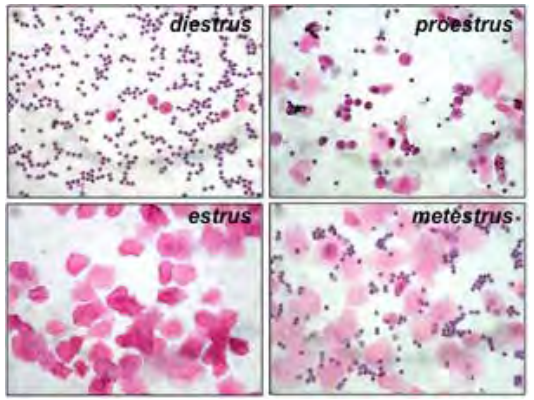
Experimental Design

- Female CD-1 mice were dosed with IAA in the drinking water for 35 days

- Control: only water
- 0.5 mg/L IAA
- 10 mg/L IAA
- 100 mg/L IAA
- 500 mg/L IAA

n= 12 per group



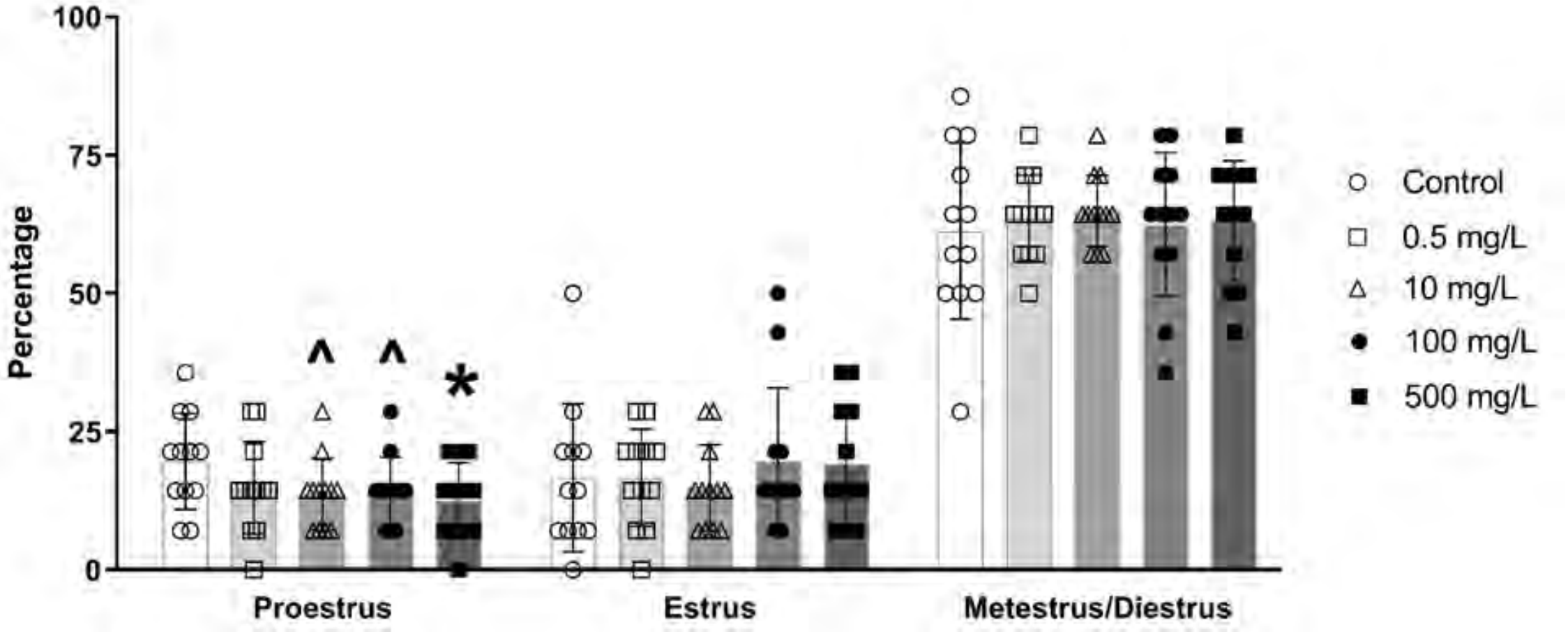


Estrous cyclicity

Ovaries for gene expression analyses

Serum for hormone analyses

IAA exposure affects estrous cyclicity

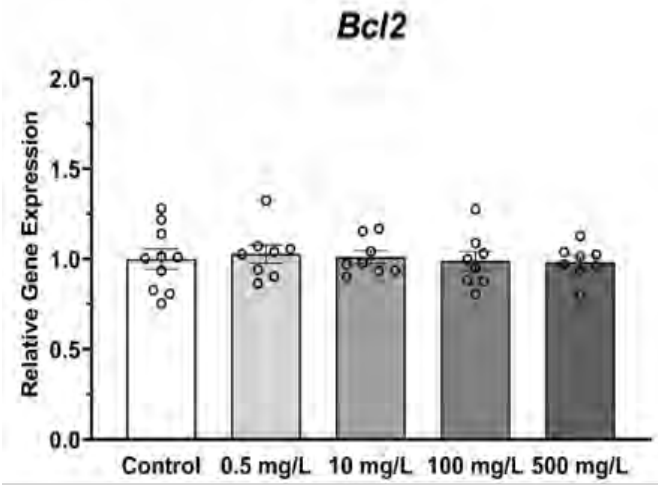


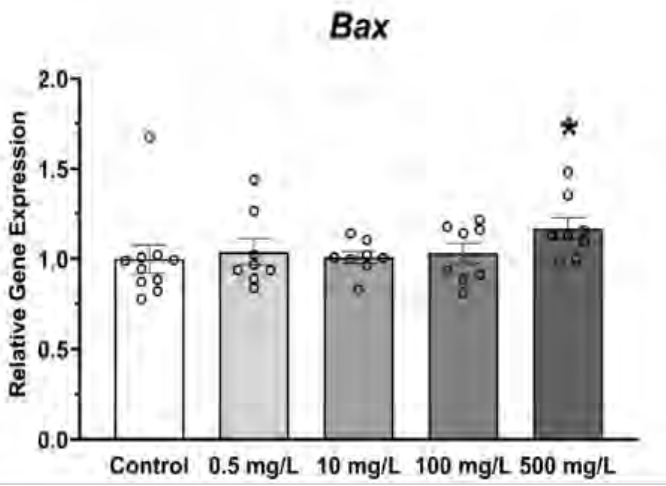
n=12, * $p \leq 0.05$, ^ $p \leq 0.096$

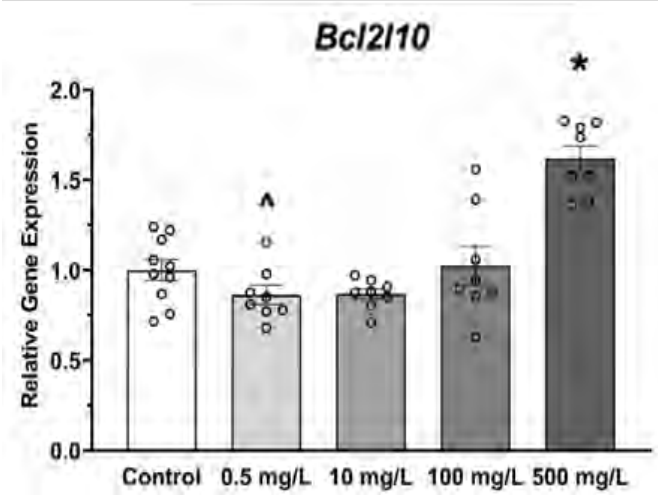
IAA exposure affects expression of apoptotic factors

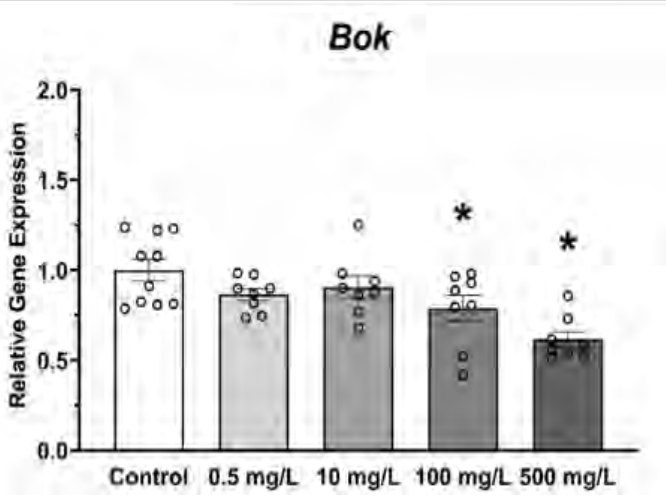
Anti-apoptotic Factors

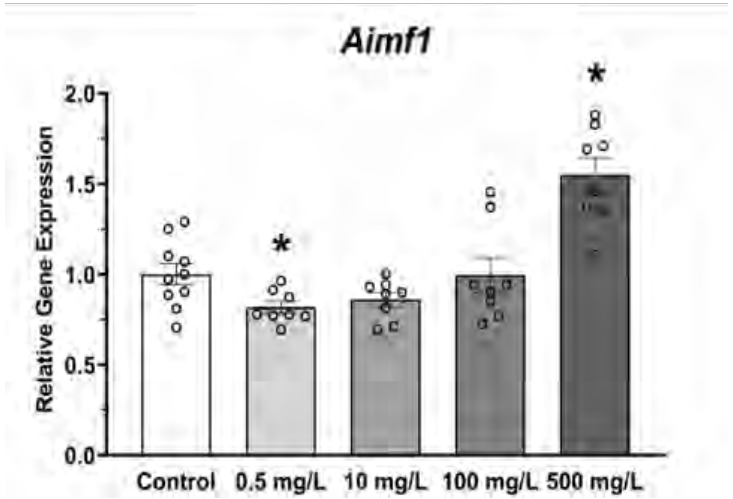
Pro-apoptotic Factors







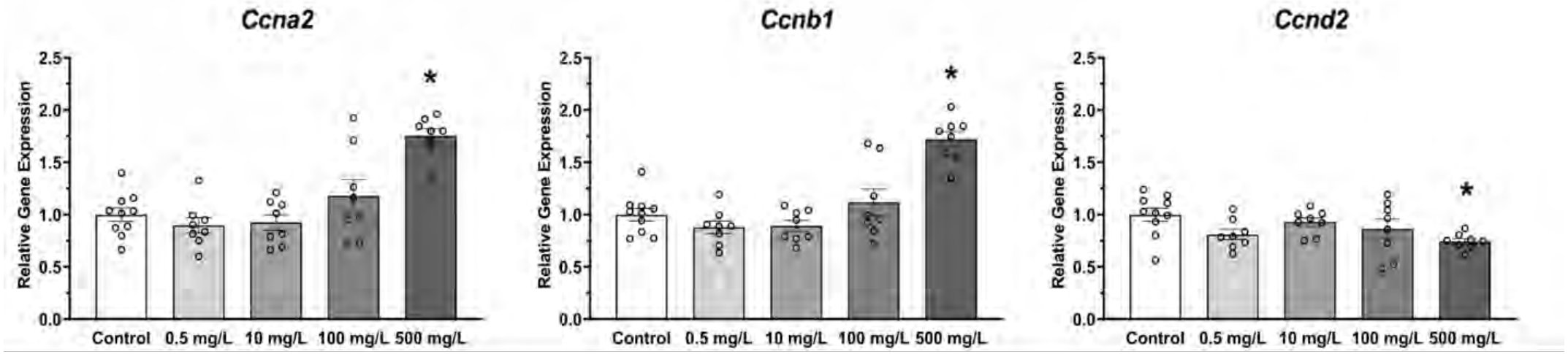


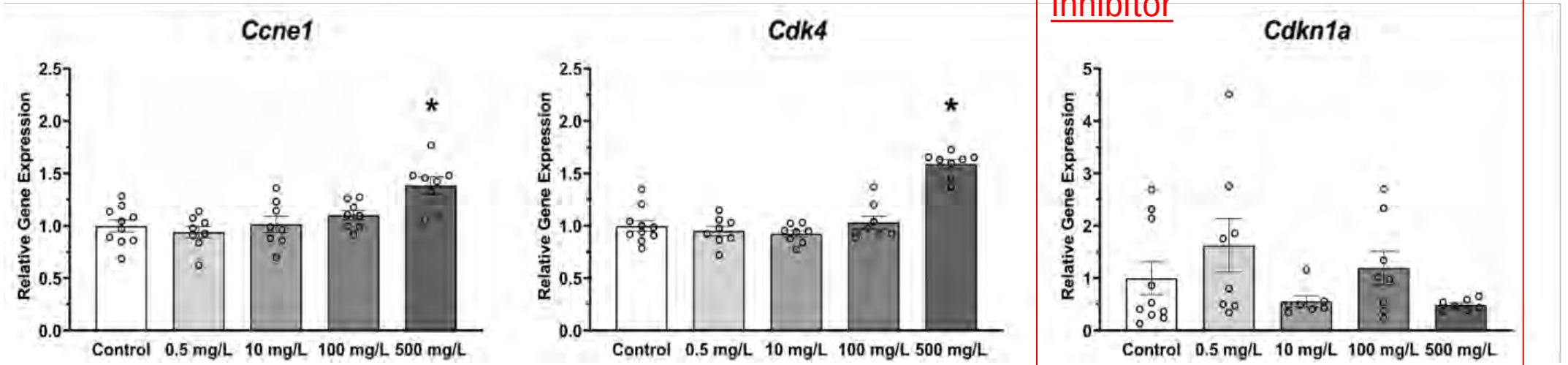


n=10-12, * $p \leq 0.05$, ^ $p \leq 0.076$

IAA exposure affects expression of cell cycle regulators

Promoters

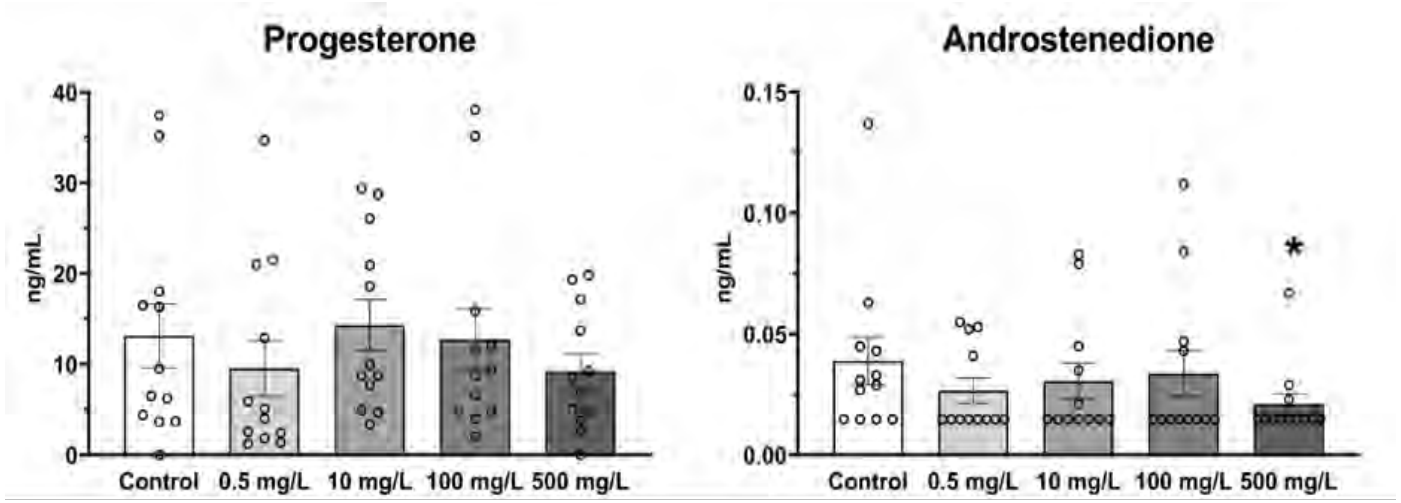


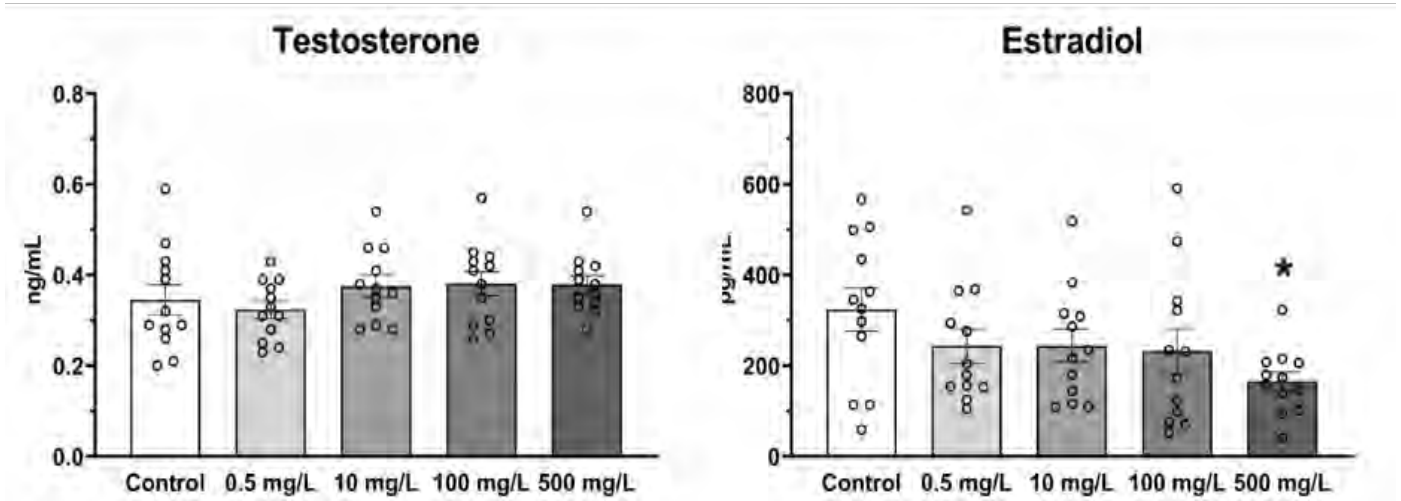


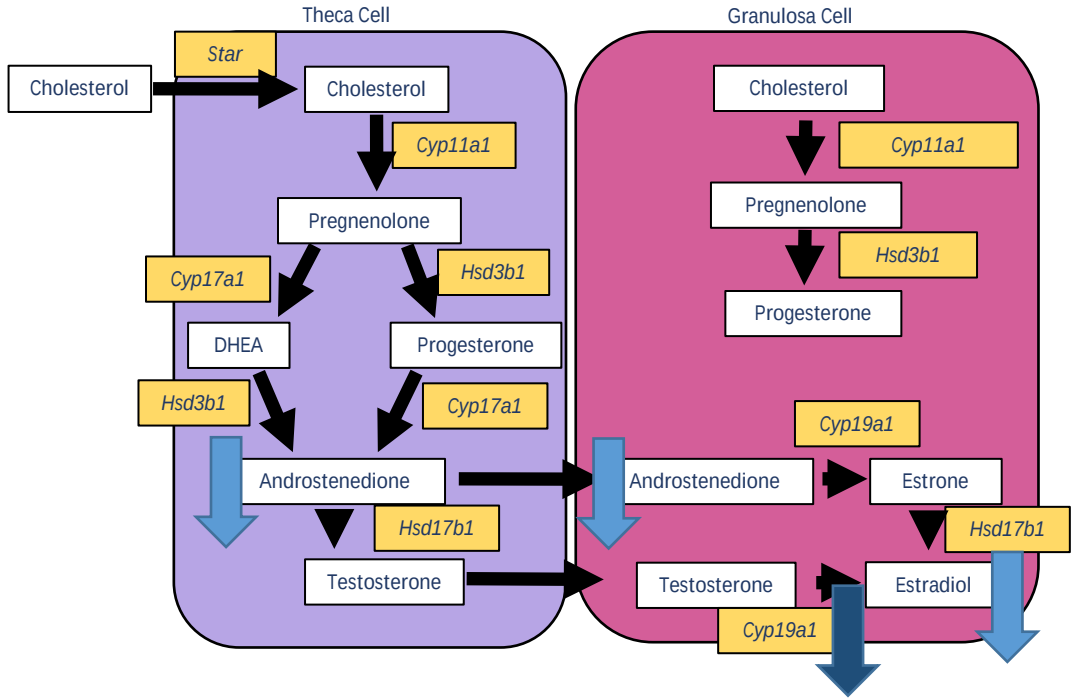
Inhibitor

n=10-12, * $p \leq 0.05$

IAA exposure affects estradiol levels







n=12, * $p \leq 0.05$

Comparison of gene expression in vitro vs. in vivo

	Gene	Antral follicles in vitro	Whole ovaries in vivo
Anti-apoptotic Factors	*Bcl2*	↓	↔
	Bcl2l10	↓	↑ ↓
Pro-apoptotic Factors	*Bax*	↑	↑
	Bok	**No Data**	↓
	Aimf1	↑	↑ ↓
Cell Cycle Promoters	*Ccna2*	↓	↑
	Ccnb1	↓	↑
	Ccnd2	↓	↓
	Ccne1	↓	↑
	Cdk4	↑	↑
Cell Cycle Inhibitor	*Cdkn1a*	↑	↔

Comparison of gene expression in vitro vs. in vivo

	Gene	Antral follicles in vitro	Whole ovaries in vivo
Steroidogenic Factors	*Star*	↑	⇔
	Cyp11a1	↑	⇔
	Hsd3b1	↑	⇔
	Hsd17b1	↓	⇔
	Cyp17a1	↓	⇔
	Cyp19a1	↓	↓

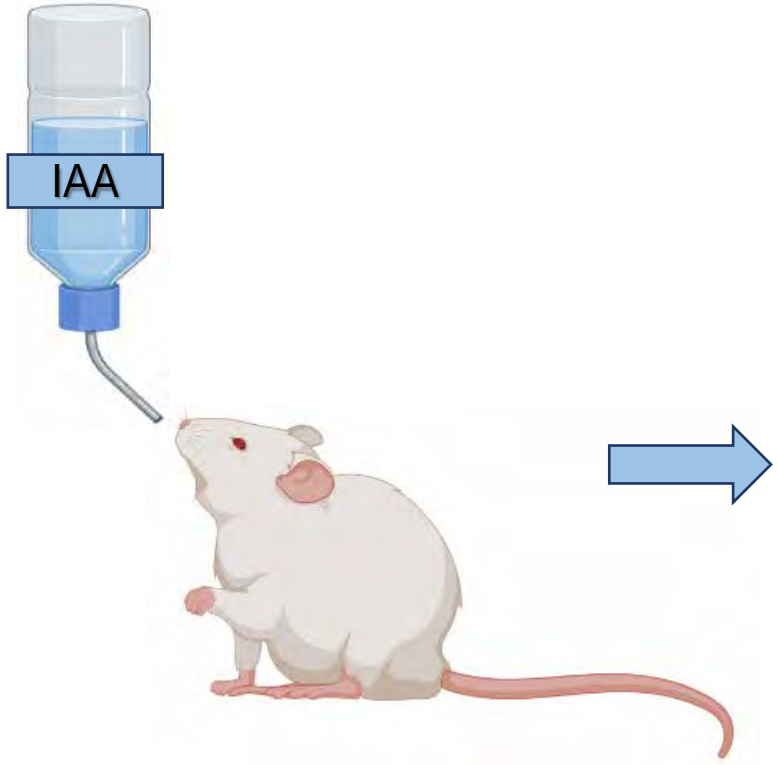
Comparison of hormone levels in vitro vs. in vivo

	Hormone	Antral Follicles In Vitro	In Vivo
Sex Steroid Hormones	*Pregnenolone*		
	Progesterone		
	Androstenedione		
	Testosterone		
	Estradiol		

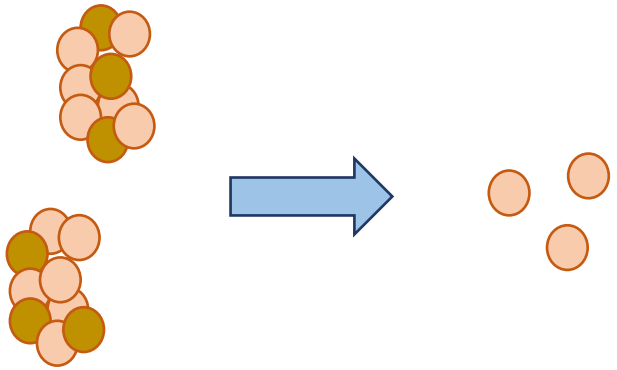
Hypothesis

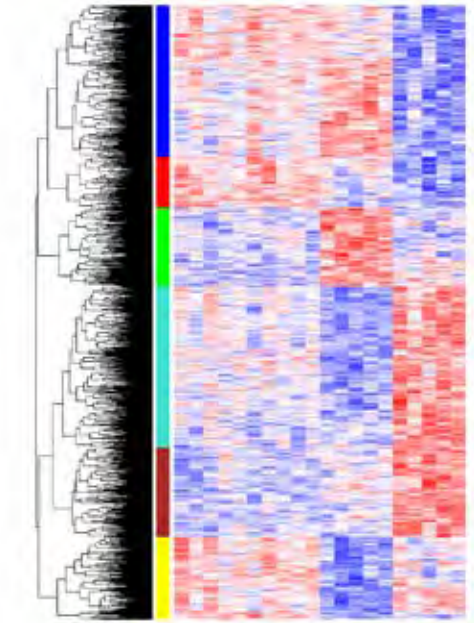
Iodoacetic acid exposure affects the transcriptome in ovarian antral follicles

Experimental Design



Isolated antral follicles





- Female CD-1 mice were dosed with IAA in the drinking water for 35 days

- Control: only water
- 10 mg/L IAA
- 500 mg/L IAA

n= 12 per group

- RNA sequencing analysis

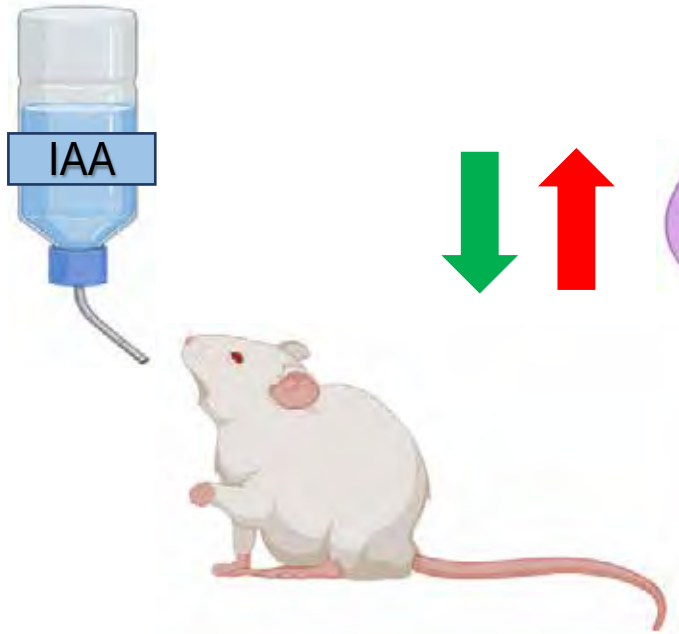
- Enrichment annotation analysis

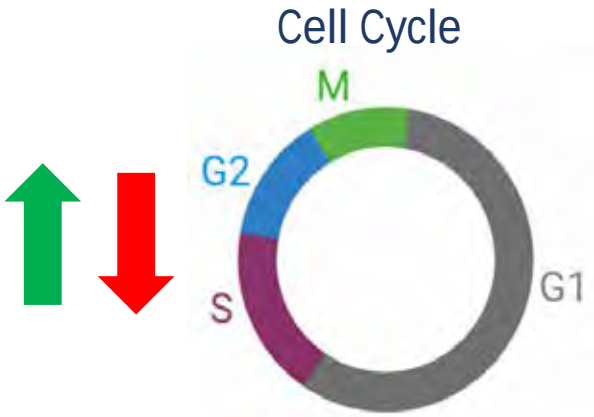
Summary

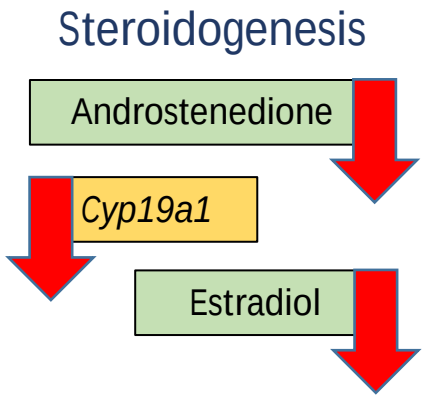
IAA exposure altered expression of genes involved with:

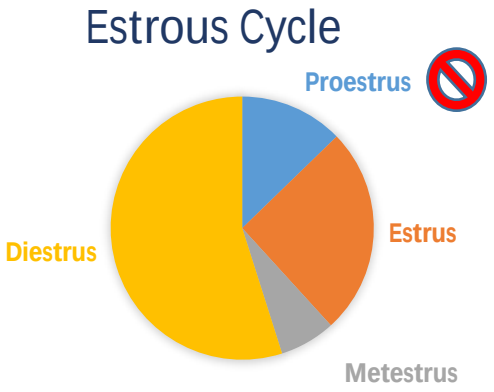
- RNA processing
- regulation of angiogenesis
- cell cycle
- mitotic cellular division
- cell division
- the PI3K-Akt signaling pathway
- the estrogen signaling pathway
- the GnRH signaling pathway
- the insulin signaling pathway
- the oxytocin signaling pathway

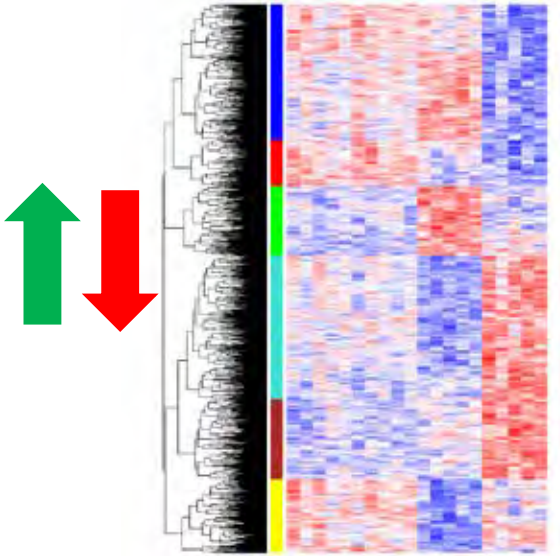
Summary (In Vivo)



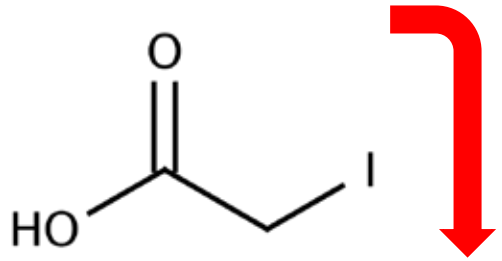




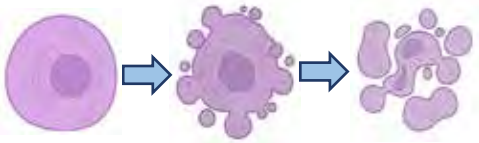


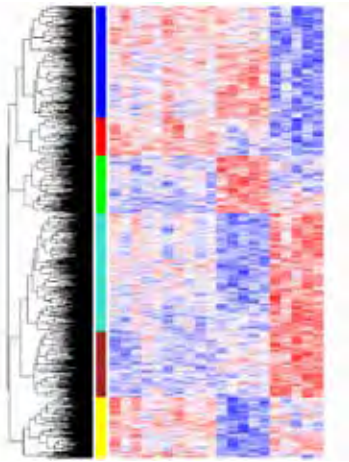


Conclusions

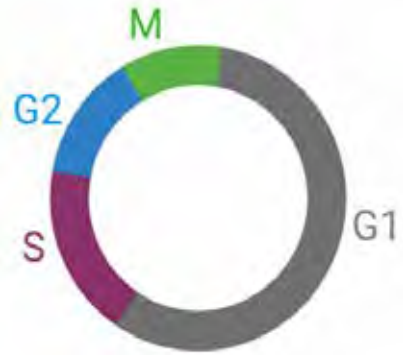


Apoptosis

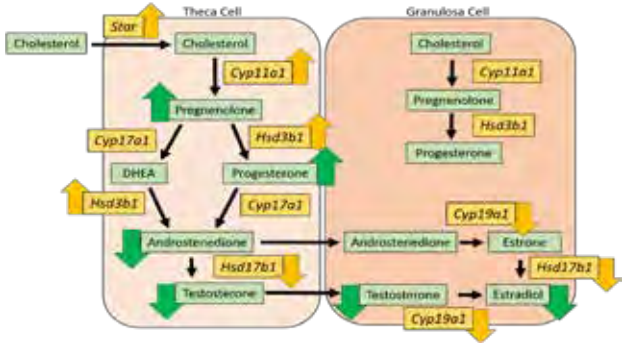




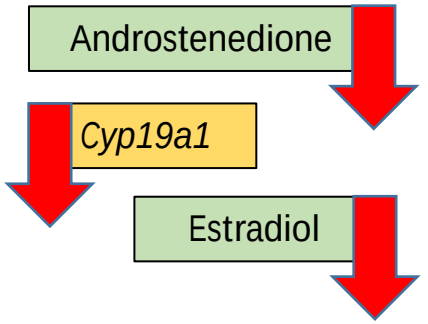
Cell Cycle



Disrupts steroidogenesis (In Vitro)

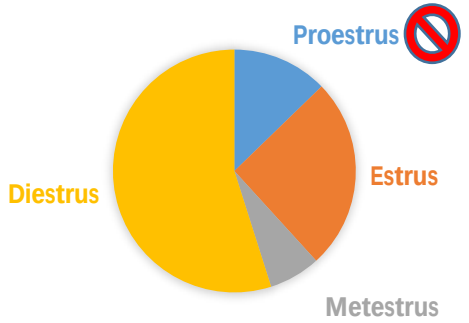


Disrupts steroidogenesis (In Vivo)



Impairs follicle growth

Disrupts estrous cycle



Acknowledgements

- Dr. Michael Plewa
- Flaws laboratory members

- Funding
  - NIH R21 ES028963
  - NIH T32 ES007326
  - Toxicology Scholarship

Questions?

Hiding In Plain Sight

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Breast Cancer Risk

Elizabeth Boham, M.D., Michele La Merrill, Ph.D., Lindsey Treviño, Ph.D.

Moderated by Deb Kilday

Elizabeth Boham, M.D.

Medical Director

The UltraWellness Center

Endocrine Disrupting Chemicals and Breast Cancer Risk

U.S. Dept of Health and Human Services

Endocrine Disrupting Chemicals and Women's Health Symposium

July 18th 2023

Outline

- Extent of the problem
- What are endocrine disrupting chemicals
- Mechanism of action
- How to avoid
- Prevention
- Phytonutrients
- What can YOU do
- What can WE do

Breast Cancer Statistics in the US in 2022

- Approximately 13% of women (1 in 8) will be diagnosed with invasive breast cancer, and 3% (1 in 39) will die from the disease in their lifetime
- In 2022 approximately
  - 287,850 new cases of invasive breast cancer
  - 51,400 cases of DCIS
  - 43,250 women die from breast cancer
  - 4.1 million women with a history of breast cancer living in the United States
- Incidence rates continue to increase
- Most common cancer in women, except for skin cancer
- Median age is 62

Giaquinto, A.N., Sung, H., Miller, K.D., Kramer, J.L., Newman, L.A., Minihan, A., Jemal, A. and Siegel, R.L. (2022), Breast Cancer Statistics, 2022. CA A Cancer J Clin, 72: 524-541. https://doi.org/10.3322/caac.21754

Causes of Breast Cancer

- Genetics – high and low penetrance genes
- Reproductive history
- Lifestyle
  - Obesity
  - Diet
  - Lack of physical activity
  - Alcohol intake
- Environmental exposures – Since WWII and increased exposure and increased incidence of breast cancer

Gray, J.M., Rasanayagam, S., Engel, C. *et al.* State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health* **16**, 94 (2017). https://doi.org/10.1186/s12940-017-0287-4

Endocrine Disrupting Chemicals What Matters?

Exposure

Timing

Genetics

Lifestyle

Endocrine Disrupting Chemicals What Matters?

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Timing

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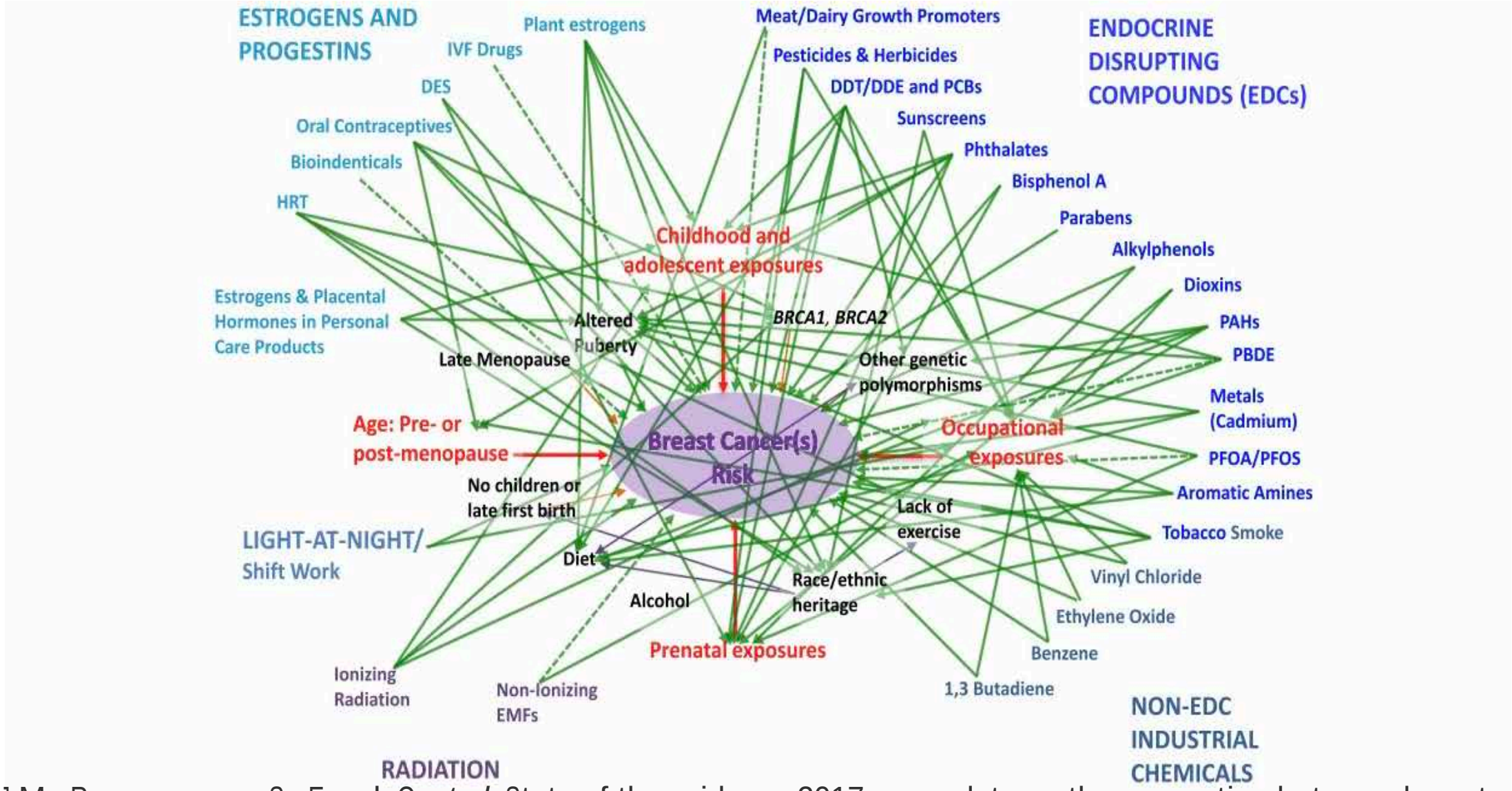
Lifestyle

Complexity of Factors Impacting Risk of Breast Cancer



Gray, J.M., Rasanayagam, S., Engel, C. *et al.* State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health* **16**, 94 (2017). https://doi.org/10.1186/s12940-017-0287-4

Endocrine Disrupting Chemicals

An exogenous chemical or mixture of chemicals that interferes with any aspect of hormone action

- BPA – bisphenol A – used in polycarbonate plastic, dental sealants, thermal receipts, food packaging and epoxy resins lining food cans
- Phthalates – fragrance ingredients in personal care and cleaning products, plastics, building materials, insecticides, food packaging, plastic wrap
- Parabens – antimicrobial preservatives in foods, personal care products, cosmetics, moisturizers, soaps, detergents and pharmaceuticals
- Alkylphenols – detergents and cleaning products
- Triclosan and triclocarban – antimicrobials in toothpaste, personal care and household products

Gray, J.M., Rasanayagam, S., Engel, C. *et al.* State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health* **16**, 94 (2017). https://doi.org/10.1186/s12940-017-0287-4

BPA

- Prenatal exposure of rats to BPA resulted in increases in the number of pre-cancerous lesions and in situ carcinomas, as well as an increased number of mammary tumors following adult exposures to sub- threshold doses of known **carcinogens**
- Neonatal **exposure** of mice to BPA **increased sensitivity** to estradiol-mediated development of mammary gland structures at puberty
- Effects of BPA on mammary tissue development may also be manifested via **epigenetic mechanisms**, leading to changes in gene regulation across the lifetime
- BPA **reduces the efficacy of common chemotherapy** agents (cisplatin, doxirubicin and vinblastin) in their blocking the proliferation of human breast cancer cells when tested in vitro
- **3-day period of limiting intake of packaged foods** decreased the concentrations of BPA found in urine by an average 65%

Gray, J.M., Rasanayagam, S., Engel, C. *et al.* State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health* **16**, 94 (2017). https://doi.org/10.1186/s12940-017-0287-4

Phthalates

- They can **bind to estrogen receptors** induce estrogen-appropriate cellular responses and act additively with estradiol in altering these systems
- Promote cancer stem cell growth
- Phthalates can also induce **proliferation, malignant invasion, and tumor formation** in breast cancer cell lines that are receptor negative, indicating that at least some effects of these compounds are independent of their direct estrogenic or androgenic effects
- Mouse studies – interfere with production of testosterone and estradiol and abnormalities in male offspring exposed prenatally included nipple retention, shortened anogenital distance and increased cryptorchidism
- BBP, DBP and DEHP all significantly increased cell proliferation in MCF-7 breast cancer cells. In addition, these three phthalates **inhibited the anti-tumor action of tamoxifen** in MCF-7 breast cancer cells. BBP also decreased the efficacy of the chemotherapeutic agents, doxorubicin and cyclophosphamide
- A dietary intervention study has demonstrated that just a **3-day period of limiting intake of packaged foods** decreased by half the concentrations of DEHP (phthalates) found in urine

Gray, J.M., Rasanayagam, S., Engel, C. *et al.* State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health* **16**, 94 (2017). https://doi.org/10.1186/s12940-017-0287-4

Others

- Forever Chemicals - PFOA / PFOS – Teflon and Gore-tex, carpet and furniture protectants
- Higher levels of these and PCBs are found in women with breast cancer
- EDCs found in sunscreens
- Polycystic Aromatic Hydrocarbons (pyrene and benzene) – byproducts of combustion – coal burners, grilled meats, cigarettes, diesel fuel
- DDE (metabolite of DDT)
  - DDT/DDE – used for malaria control – still used in sub- Sararan Africa
  - Clear association when looking at early life (prenatal and childhood) exposure -
- Triazine herbicides (ie atrazine) –
  - shown to increase aromatase activity
  - exposure in rats during pregnancy let to changes in mammary gland of pups

Endocrine Disrupting Chemicals What Matters?

Exposure

Timing

Genetics

Lifestyle

Timing of Exposure

- We need to think about timing of exposure – ie fetal and adolescent exposure and later developing the disease
- Long latency between exposures and diagnosis
- Earlier developmental exposures can be especially powerful in affecting development of breast cancer, even decades later
- EDC disrupt the endocrine system – does not follow the typical linear dose relationship
- Even at low dose they may impact health at critical periods

Gray, J.M., Rasanayagam, S., Engel, C. *et al.* State of the evidence 2017: an update on the connection between breast cancer and the environment. *Environ Health* **16**, 94 (2017). https://doi.org/10.1186/s12940-017-0287-4

Timing of Exposure – Examples

- For BPA most profound impact is exposure during early development
- Prenatal and neonatal exposure to BPA (bisphenol A) can change mammary tissue development and impact likelihood of development of mammary tumors later in life
- DES (diethylstilbestrol) exposure increased risk of breast cancer in daughters and granddaughters
  - Impacts that mammary gland epigenome through alterations in histone methylation – leading to altered gene expression in puberty and adulthood
  - Epigenetic changes could be the mechanism for trans-generational effects
- Higher maternal DDT (dichlorodiphenyl trichloroethane) levels were associated with 4 x increase risk of breast cancer in daughters by at 52
- Exposure to radiation in childhood and adolescence increases risk for breast cancer later in life

Endocrine Disrupting Chemicals What Matters?

Exposure

Timing

Genetics

Lifestyle

Endocrine Disrupting Chemicals What Matters?

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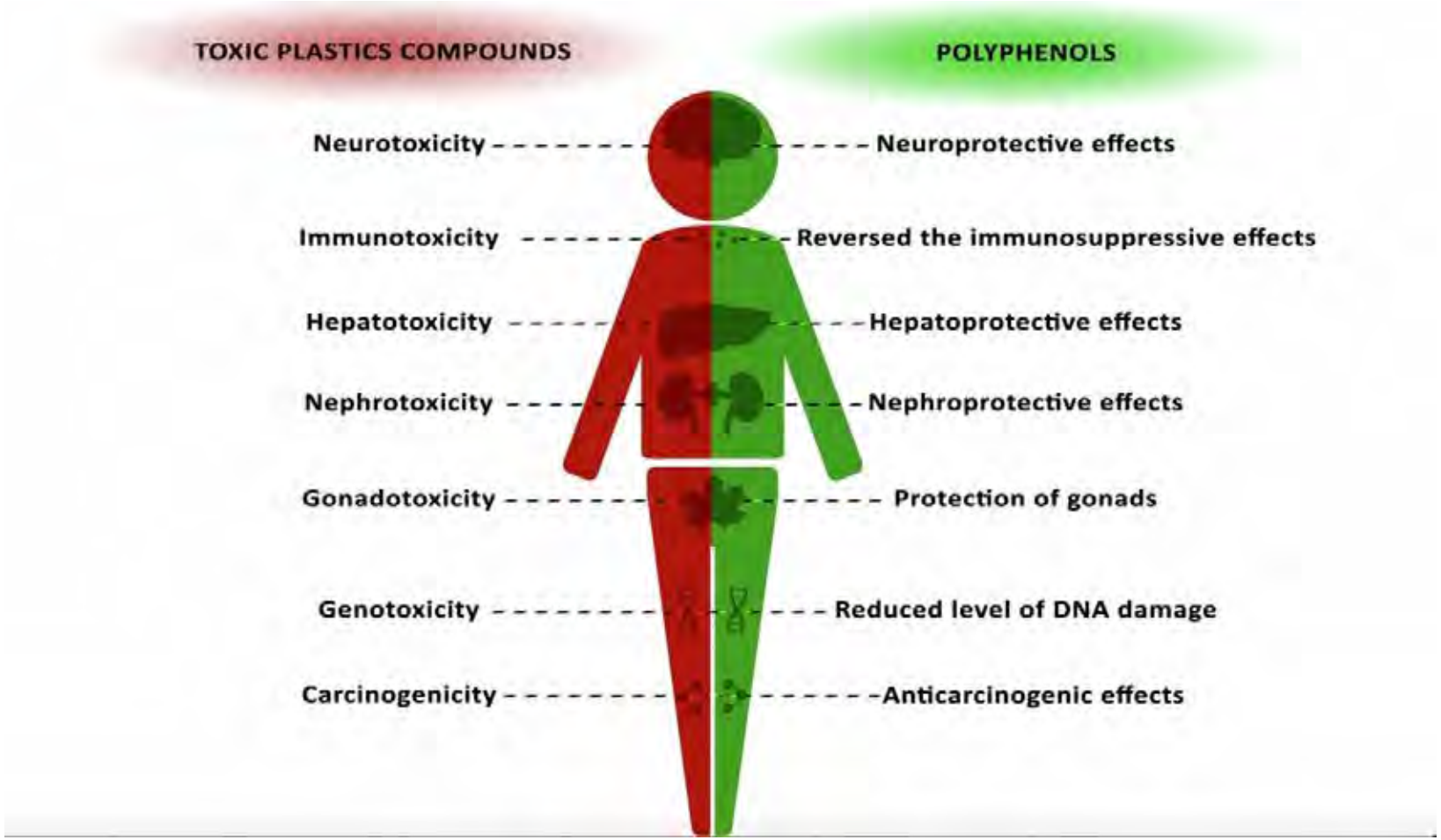
The influence of polyphenols on metabolic disorders caused by compounds released from plastics - Review



Żwierełło, W. (2020). The influence of polyphenols on metabolic disorders caused by compounds released from plastics – Review. *Chemosphere*, 240. https://doi.org/10.1016/j.chemosphere.2019.124901.

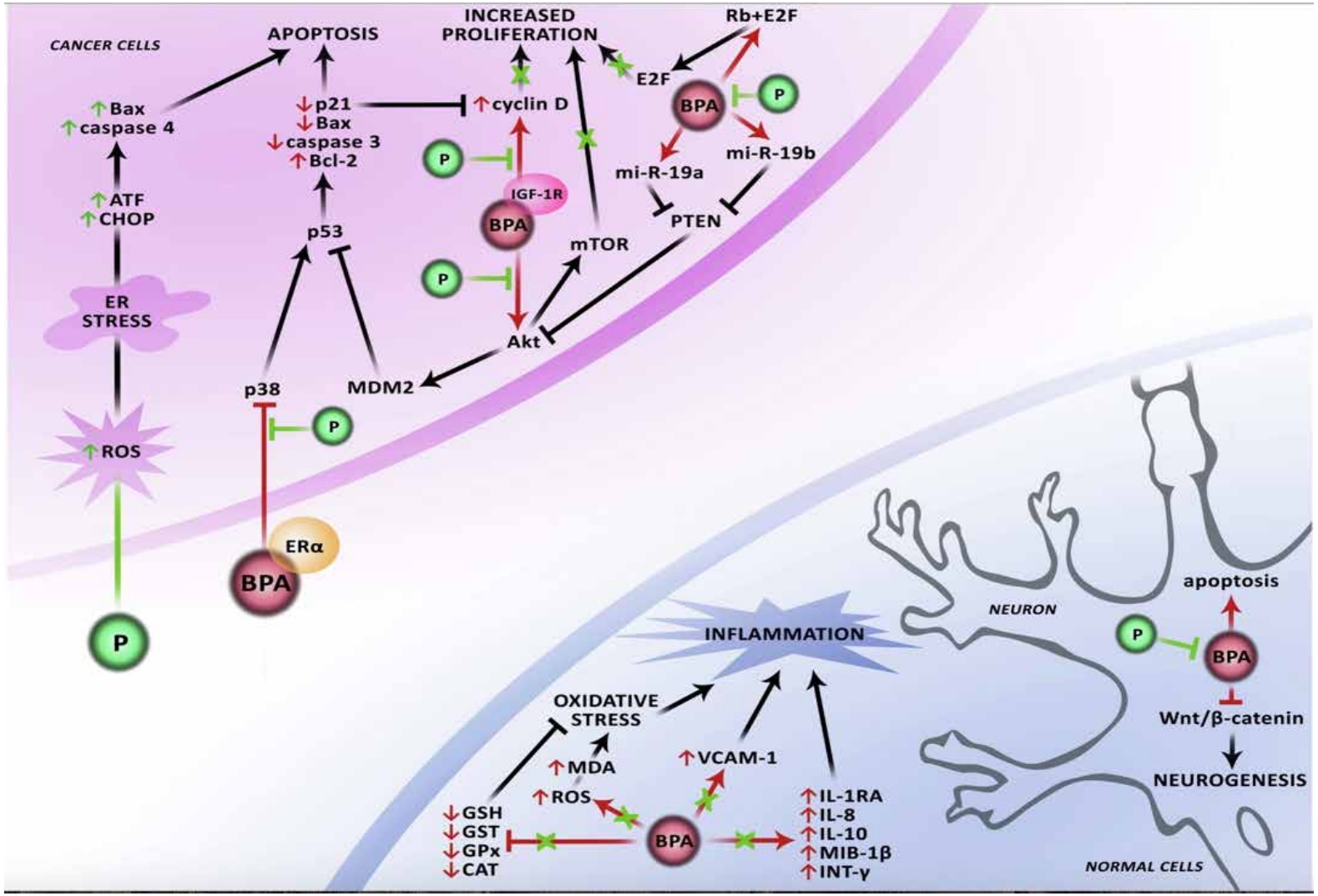
The influence of polyphenols on metabolic disorders caused by compounds released from plastics - Review

Highlights

- Toxic substances released from plastics pose environmental pollution.
- Plastic compounds induce e.g. oxidative stress, apoptosis and inflammation.
- Toxic plastic compounds may promote cancer progression and metastasis.
- Polyphenols exert protective effect against ACN, PCBs, BPA, phthalates and dioxins.
- Polyphenols inhibit cancer progression and metastasis promoted by plastics compounds.

Żwierełło, W. (2020). The influence of polyphenols on metabolic disorders caused by compounds released from plastics – Review. *Chemosphere*, 240. https://doi.org/10.1016/j.chemosphere.2019.124901.

Polyphenols Negate toxicity of BPA



Żwierełło, W. (2020). The influence of polyphenols on metabolic disorders caused by compounds released from plastics – Review. *Chemosphere*, 240. https://doi.org/10.1016/j.chemosphere.2019.124901.

Phytonutrients

Phytonutrients - plant metabolites that defend against microbes

- Increase host defense against DNA damaging molecules. Reduce oncogenic potential of carcinogens.
- Organic has more phytochemicals and mineral content
  - Plant under stress

Czech A, Szmigielski M, Sembratowicz I. Nutritional value and antioxidant capacity of organic and conventional vegetables of the genus Allium. Sci Rep. 2022 Nov 4;12(1):18713. doi: 10.1038/s41598-022-23497-y. PMID: 36333512; PMCID: PMC9636188.

THINK COLOR!

- Chlorophyll – green vegetables
- Glucosinolates – cruciferous vegetables
- Xanthophyll – yellow carotenoid pigment
- Isoflavones – phytoestrogen
- Polyphenols – quercetin, lignan, flavonoids
- Flavonoids – Catechins, ECGC = epigallocatechin
- Carotenoids – yellow / orange
- **8 - 10 ½ cups PER DAY**
- **8 - 12 servings Per Day**

Isoflavones

- Phytoestrogens = Anti-estrogen
- Genistein
- Daidzein
- Equol – secondary metabolite of soy made in gut from healthy microbiota

Soy and Flax

- Phytoestrogens – weak estrogenic activity – block / antagonize the impact of estrogen
- Lignans – seeds and grains - flax, pumpkin, sunflower, poppy, sesame, whole grains (rye, oat, barley) and tofu.
- Association with lignan intake and a lower risk of breast cancer, especially in postmenopausal women on hormone therapy.
- Flax seeds
  - highest concentration of lignans
  - alpha – linolenic acid - rich in omega 3 fats

https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/lignans#reference9

Wang X.. Exploring the Biological Activity and Mechanism of Xenoestrogens and Phytoestrogens in Cancers: Emerging Methods and Concepts. Int J Mol Sci. 2021 Aug 16;22(16):8798. doi: 10.3390/ijms22168798. PMID: 34445499; PMCID: PMC8395949.

The Shanghai Breast Cancer Survival Study

ORIGINAL CONTRIBUTION

Soy Food Intake and Breast Cancer Survival

Xiao Ou Shu, MD, PhD
Ying Zheng, MD, MSc
Hui Cai, MD, PhD
Kai Gu, MD
Zhi Chen, MD, PhD
Wei Zheng, MD, PhD
Wei Lu, MD, PhD

Among women with breast cancer, soy food consumption was significantly associated with **decreased risk of death and recurrence**.

The inverse association was evident among women with either ER-positive or ER-negative breast cancer and was present in both users and non-users of tamoxifen.

This study suggests that moderate soy food intake is **safe and potentially beneficial** for women with breast cancer.

Shu, X. JAMA, 2009;302:2437-43.

For editorial comment see p 2483.

Author Affiliations: Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center and Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, Tennessee (Drs Shu, Cai, Chen, and W. Zheng); and Shanghai Institute of Preventive Medicine, Shanghai, China (Drs Y. Zheng, Gu, and Lu).
Corresponding Author: Xiao Ou Shu, MD, PhD, Department of Medicine, Vanderbilt Epidemiology Center, 2525 West End Ave, Ste 600, Nashville, TN 37203-1738 (xiao-ou.shu@vanderbilt.edu).

What can you do to lower your toxin load?

- Buy organic
  - Decreased pesticide exposure
  - Decreased growth hormone exposure
- Use glass whenever possible
- Store food in glass
- Do not heat or microwave plastic
- Limit processed / packaged foods
- Cook More
- Improve our diet
  - Increase nutrient dense whole foods, fiber and phytonutrients
- Switch to glass / stainless steel reusable water bottles
- Read labels on personal care products
- Use unscented lotions, laundry detergents and cleaning supplies
- Avoid herbicides / pesticides on your lawn and garden
- Environmental Working Group – www.ewg.org
- Think Dirty App – www.thinkdirtyapp.com

What Can We Do

- Collect data on whole life exposure to EDCs
- Move away from packaging containing EDCs in favor of biodegradable products
- Adopt policy to restrict EDCs
- Transform how federal dollars are used to support food as medicine (foodfix.org)
  - Incentivize Regenerative Organic Agriculture
  - Reimagine agricultural practices, nutrition, and health
  - Improve food supply so more people have access to healthful foods

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Breast Cancer Risk

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Department of Environmental Toxicology
Environmental Health-, Comprehensive Cancer-, and Genome- Centers
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The International Agency for Research on Cancer (IARC) is the world's authority on carcinogens

- IARC is part of the World Health Organization
- IARC classifies carcinogens based upon available scientific information
  - These classifications make up volumes called Monographs
- Experts without conflicts of interest from all over the world evaluate the scientific information
- Classification is based on the weight of scientific evidence
  - human evidence weighted most heavily

IARC Classifications Framework

Table 4. Integration of streams of evidence in reaching overall classifications (the evidence in *bold italic* represents the basis of the overall evaluation)

Stream of evidence			Classification based on strength of evidence
Evidence of cancer in humans[a]	**Evidence of cancer in experimental animals**	**Mechanistic evidence**	
Sufficient	Not necessary	Not necessary	**Carcinogenic to humans (Group 1)**
Limited or Inadequate	***Sufficient***	***Strong (b)(1) (exposed humans)***	
Limited	***Sufficient***	Strong (b)(2–3), Limited, or Inadequate	**Probably carcinogenic to humans (Group 2A)**
Inadequate	***Sufficient***	***Strong (b)(2) (human cells or tissues)***	
Limited	Less than Sufficient	***Strong (b)(1–3)***	
Limited or Inadequate	Not necessary	***Strong (a) (mechanistic class)***	
Limited	Less than Sufficient	Limited or Inadequate	**Possibly carcinogenic to humans (Group 2B)**
Inadequate	***Sufficient***	Strong (b)(3), Limited, or Inadequate	
Inadequate	Less than Sufficient	***Strong b(1–3)***	
Limited	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	
Inadequate	***Sufficient***	***Strong (c) (does not operate in humans)***[b]	**Not classifiable as to its carcinogenicity to humans (Group 3)**
All other situations not listed above			

Cancer – Can Any Thing Cause It?

Agents Classified by the IARC Monographs, Volumes 1–131

Group 1	Carcinogenic to humans	121 agents
Group 2A	Probably carcinogenic to humans	93 agents
Group 2B	Possibly carcinogenic to humans	320 agents
Group 3	Not classifiable as to its carcinogenicity to humans	501 agents

Some of the IARC Group 1 Human Carcinogens

Some of the 121 Chemicals Listed by IARC as Carcinogens to People

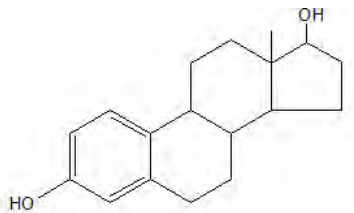
Note that in many cases data on cancer rates were collected under exposure conditions that no longer exist.

Some Occupational Exposures
- Boot and shoe manufacture (certain exposures)
- Furniture manufacture (wood dusts)
- Nickel refining
- Rubber industry (certain occupations)
- Underground hematite mining, when radon exposure exists.

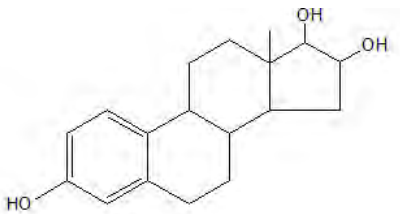
Some Chemicals
- Arsenic and arsenic compounds
- Asbestos (when inhaled)
- Chromium and certain chromium compounds (when inhaled)
- Benzene
- Diethylstilbestrol (DES)
- 2-Napthylamine, benzidine (starting materials for manufacture of certain dyes)
- Vinyl chloride (starting material for PVC plastic manufacture)
- Mustard gas

Some Chemical Mixtures
- Tobacco smoke
- Smokeless tobacco products
- Soots, tars, mineral oils*
- Analgesic mixtures containing phenacetin

* Mineral oils now in commercial production generally do not have the PAH content they had at the time the evidence of carcinogenicity was gathered.

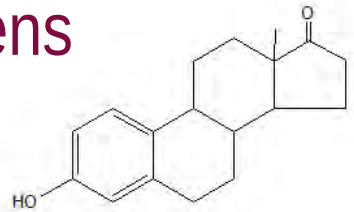


17β-Estradiol



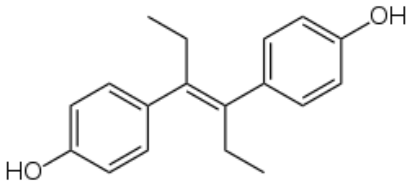
Estriol

Estrogens



Estrione

Diethylstilbesterol (DES)



Classifications by breast cancer site with sufficient or limited evidence in humans in IARC Monographs Volumes 1-133

Carcinogenic agents with *sufficient evidence* in humans	**Agents with *limited evidence* in humans**
Alcoholic beverages	Dieldrin, and aldrin metabolized to dieldrin
Diethylstilbestrol (DES)	Digoxin
Estrogen–progestogen oral contraceptives (combined)	Estrogen therapy, postmenopausal
Estrogen–progestogen menopausal therapy (combined)	Ethylene oxide
X- and Gamma-radiation	Night shift work
	Polychlorinated biphenyls
	Tobacco smoking

https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf

Adapted from Table 4 in Cogliano *et al.* (2011); available from: http://jnci.oxfordjournals.org/content/early/2011/12/11/jnci.djr483.short?rss=1

All* the known risk factors for breast cancer are linked to total lifetime exposure to estrogen

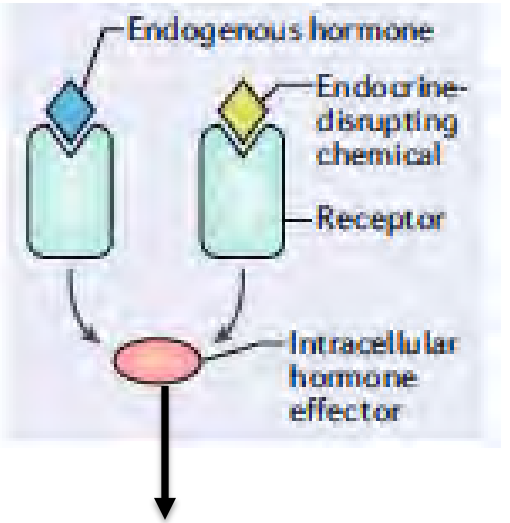
- Early puberty (periods before age 12)
- Late menopause (end of periods after age 55)
- Excess body fat (fat cells make estrogen)
- Alcohol (increases estrogen levels)
- DES (pretends to be estrogen)

*Radiation is a well- established environmental cause of breast cancer in men and women that has no clear link to estrogen

75% of human breast cancer is ER positive

ER positive means the
cancer cells have the estrogen receptor (ER)

Estrogen receptor (green) in the cancer cells
can be activated by
natural estrogen (blue diamond) or
endocrine disrupting chemicals
(EDCs, yellow diamond)



Activated ER
causes cancer growth

GROWTH OF CANCER CELLS AND
CELLS THAT MAKE BLOOD VESSELS

Diethylstilbestrol (DES)

- Synthetic form of estrogen
- Used to promote fetal growth and prevent miscarriage
- From 1938-1971 about 10 million women were exposed to DES when pregnant
- In 1971, the Food & Drug Administration (FDA) advised physicians to stop prescribing DES to pregnant women
  - because it was linked to a rare vaginal cancer in female offspring

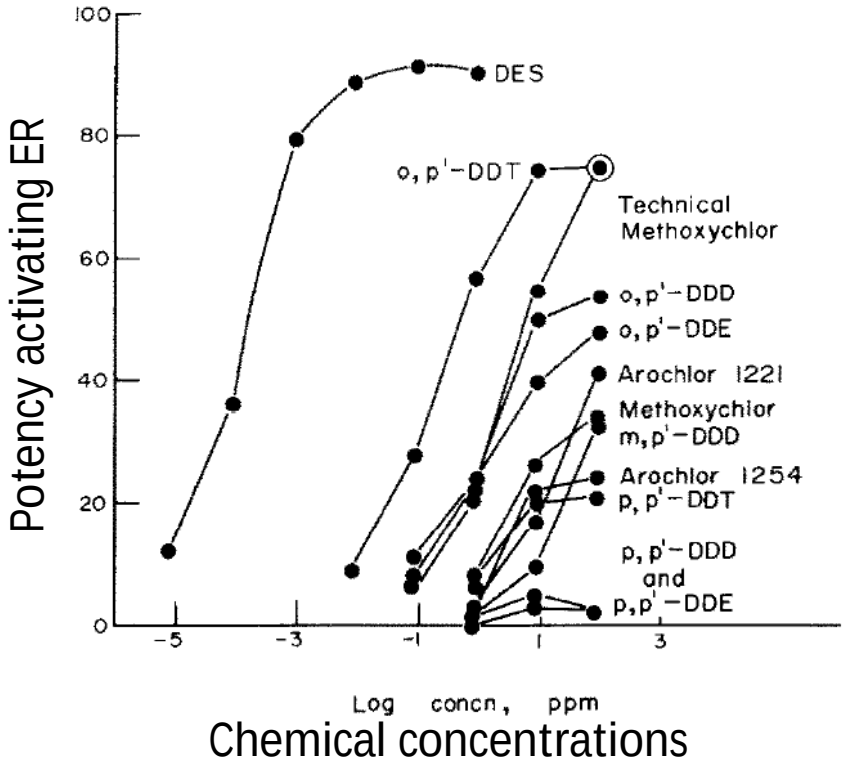
Reproductive risk associated with DES

- The women who took DES when pregnant
  - 30% increased risk of breast cancer
- Their daughters
  - Reproductive tract and breast cancers
  - Structural defects in reproductive tract
  - Preterm delivery
  - Infertility
- Their sons
  - Reproductive tract cysts
  - Structural defects in reproductive tract
  - Infertility
- Their grandkids
  - Structural defects in reproductive tract
  - Reproductive tract cancers in mice of this generation

DES is a synthetic estrogen.
Can other chemicals that
mimic estrogens result in similar
reproductive health adversities?

(A lot of toxicologists spend their careers investigating this)

Can we identify chemicals that increase risk of breast cancer by measuring if the chemicals activate ER?

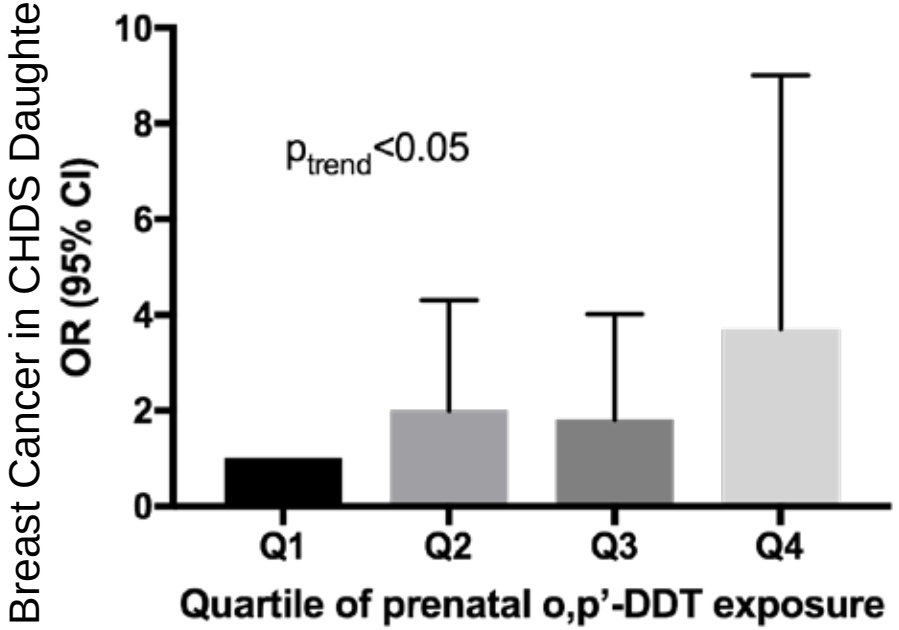


Chemical concentrations

- What does IARC say?
  - "no clear association was found between breast cancer and DDT or DDE…in adulthood"
  - the possible importance of early-life exposure to DDT remains unresolved

Child Health and Development Studies: breast cancer risk that is hard to study

- ~15,000 pregnant women in the Kaiser Permanente Health Plan joined the CHDS in 1960s.
- Early-life exposure to DDT in pregnant women associated with their increased risk of breast cancer
- Daughters had higher risk of breast cancer
- Granddaughters (in their 20s now) had earlier periods



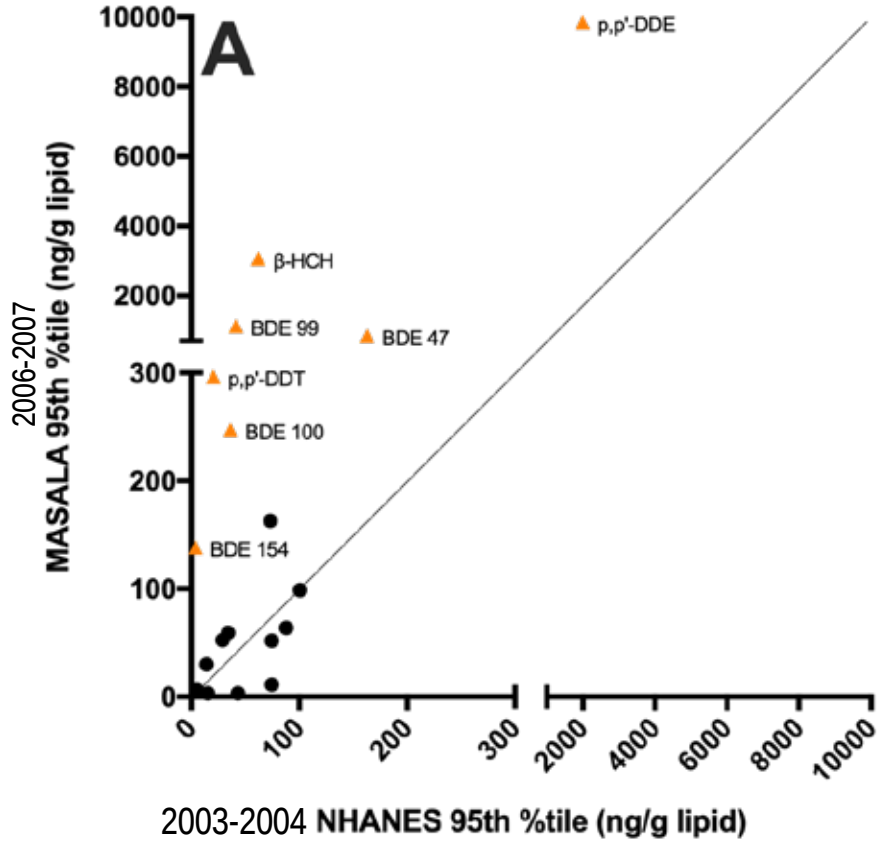
Cohn et al. 2019; Cohn, La Merrill et al. 2015; Cirillo, La Merrill et al. 2021

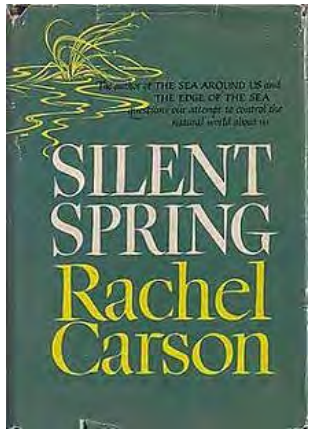
Cancer Hotspots

- Cancer Hotspot
  - A community has excess cases of cancer than expected by historical cancer data
- Breast cancer hotspots
  - Breast cancer mortality risk in hotspots linked to estrogenic exposures
    - Marin county, CA
      - Higher hormone replacement therapy (IARC sufficient evidence)
    - Long Island
      - Higher DDT

Ongoing DDT relevance in the USA:

Indian Asians living in USA have much higher levels of DDT and DDE than the "representative" US population



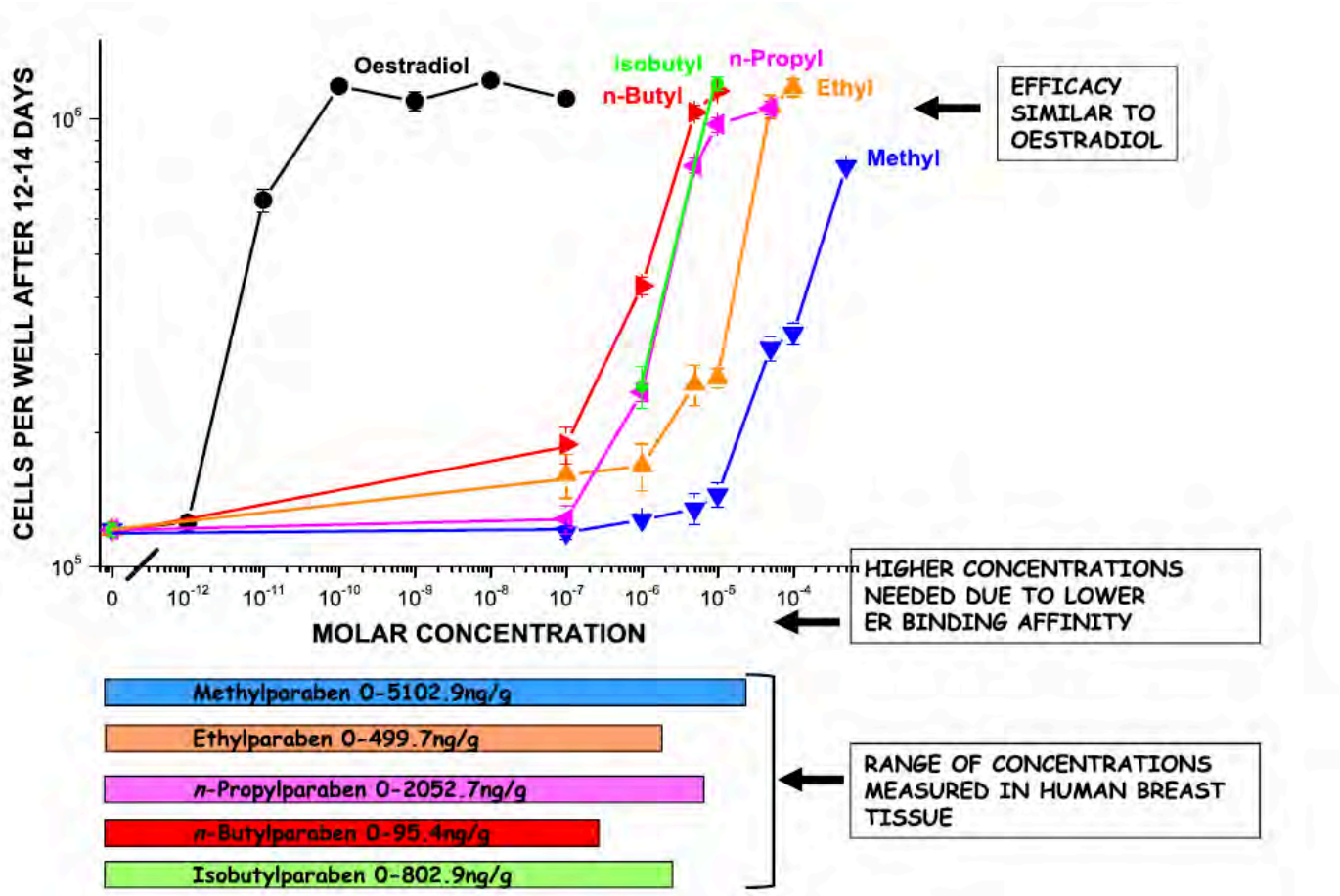


"We spray our elm trees and the following springs are silent of robin song… because the poison traveled"

La Merrill et al. 2019; Photographer: Alfred Eisenstaedt; National Portrait Gallery, Smithsonian Institution

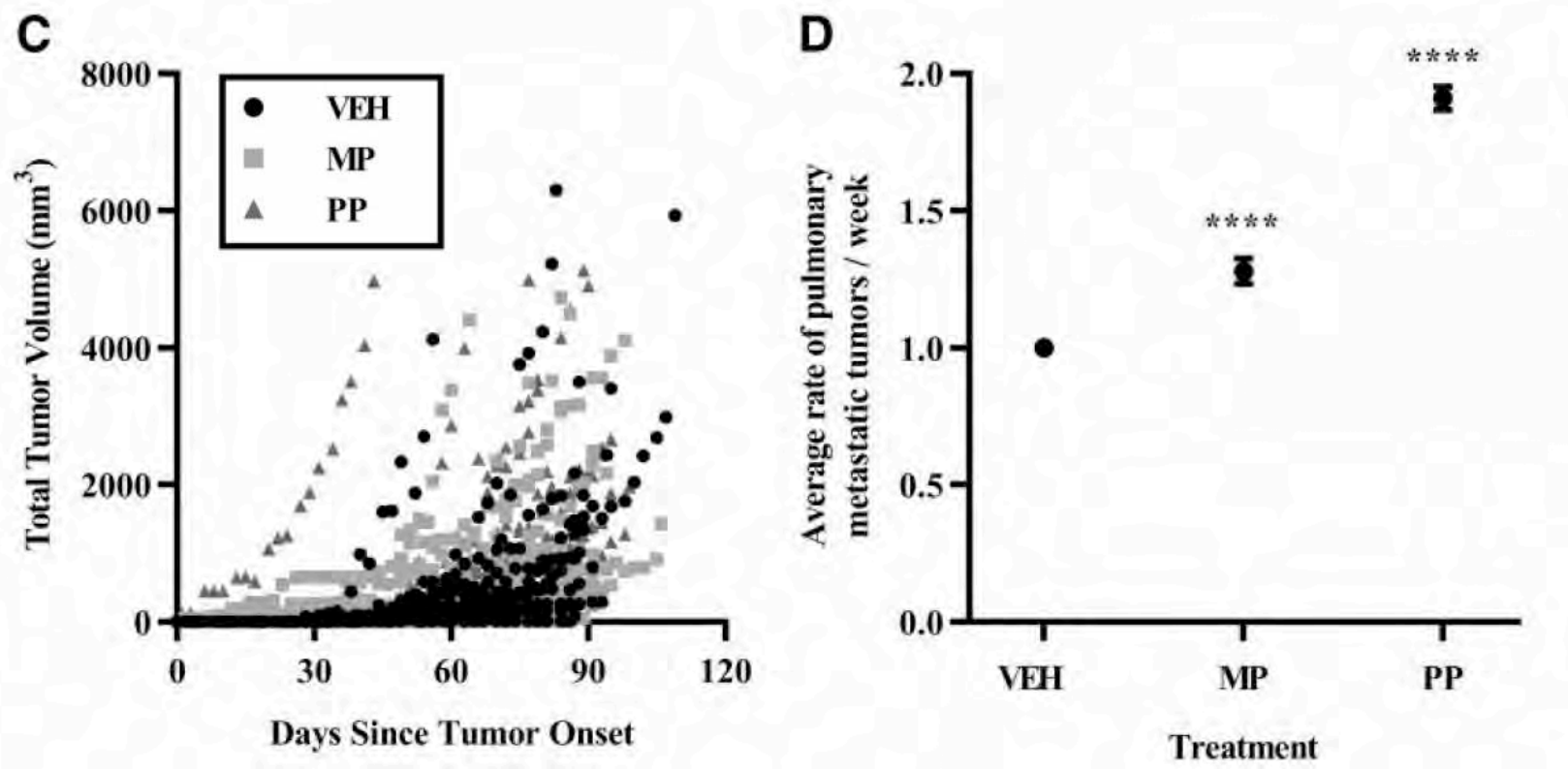
Can we identify chemicals that increase risk of breast cancer by measuring if the chemicals activate ER?

Parabens activate ER-dependent growth of human breast cancer cells



Khanna and Darbre 2013; **Darbre and Harvey 2014 (MCF-7);** Okubo et al. 2001 (MCF-7, all parabens inhibited by estrogen blocking ICI182,780)

Methylparaben and propylparaben increased the rate of breast tumor growth and its metastasis in mice



Tong et al. 2022

What can we do to reduce risk of breast cancer?

- IARC Carcinogenic agents with sufficient or limited evidence for their associations with human breast cancer
  - Drink less alcohol
  - Smoke less tobacco
  - Fly less to minimize radiation exposure
  - Consider contraceptives and menopause therapies that don't contain estrogen
  - Eat lower on the food chain since levels of 'limited evidence' agents magnify in animal fats up the food chains
    - Covers potential risk from DDT too
    - Also better for reducing your foot print on climate change
- Experimental studies in rodents and in human cells indicate that environmental chemicals that activate ER increase risk of breast cancer
  - Need human studies to confirm
  - Human studies can be very difficult due to long time for cancer to arise and other difficulties with measuring chemical exposures
- Precautionary principle can be implemented while we wait for the science to fill in the research gaps
  - Read the label with care
  - Look for phrase "paraben-free"
  - Avoid ingredients: paraben, estrogen, estrone, estriol
  - Avoid products that contain placental extracts
    - Estrogen and other hormones are present in animal placenta

Breast Cancer Risk

Lindsey Treviño, Ph.D.

Assistant Professor, Division of Health Equities and
Department of Population Sciences

City of Hope

Break

We will resume at 3:10 PM

Maternal-Child Health Risks and Risk Reduction

Carmen Messerlian, Ph.D., Rita Strakovsky, Ph.D., R.D., Christine Langton, Ph.D.

Moderated by Deb Kilday

Maternal-Child Health Risks and Risk Reduction

Carmen Messerlian, Ph.D.

Assistant Professor

Environmental Reproductive, Perinatal, and Pediatric Epidemiology

Beyond Pregnancy – How the Environment Shapes Women's Health

Carmen Messerlian, PhD

Harvard Chan School of Public Health

Endocrine Disrupting Chemicals and Women's Health Symposium

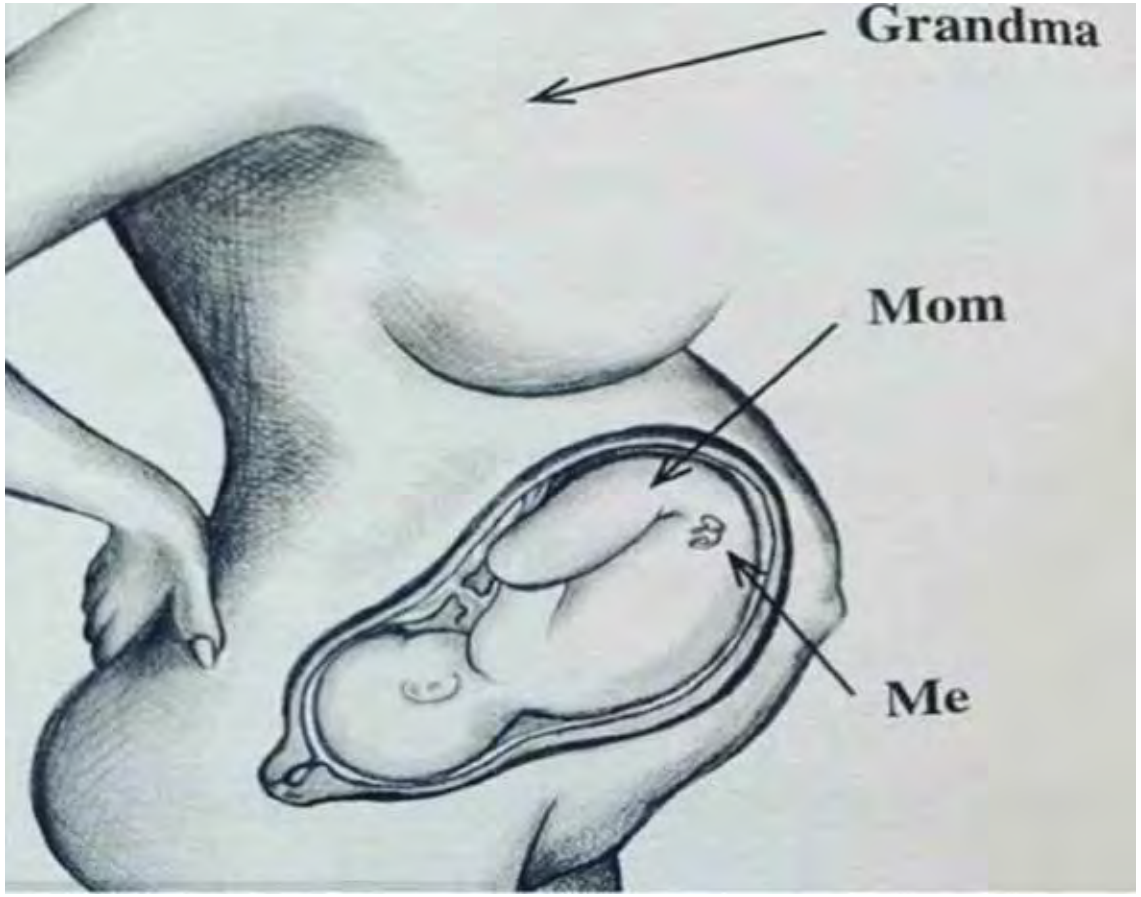
July 18, 2023

SEED PROGRAM
SCIENTIFIC EARLY LIFE ENVIRONMENTAL HEALTH & DEVELOPMENT PROGRAM

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

MGH 1811

The Origins of Reproductive Health



F0

F1

F2

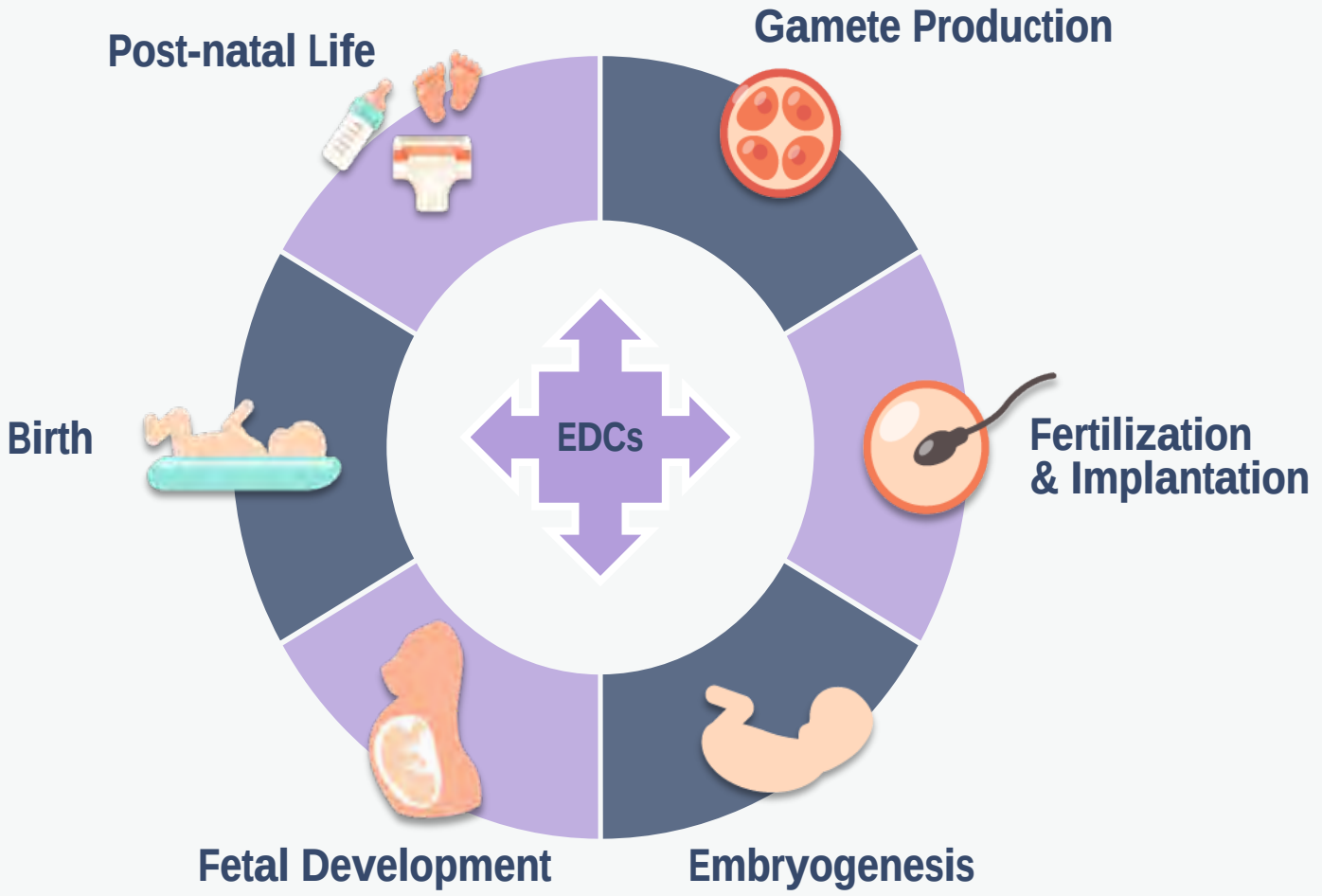
F3+

Multi-generational inheritance

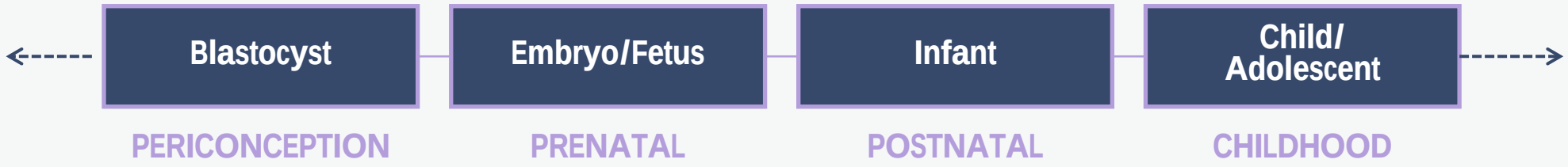
Inter-generational inheritance

The Reproductive Cycle

- Complex hormonal, molecular processes work in synchrony
- Control and interplay – organs, tissues, cells
- Timing of events - disruption
- Opportunity for adaptation or aberration



Timing of Exposure



Adapted from: TJ Woodruff, SJ Janssen, LJ Guilllette Jr, L Giudice. (2010). Environmental Impacts on Reproductive Health and Fertility. Cambridge University Press.

Preconception Origins of Health and Disease

Most studies focus on *in utero* exposure

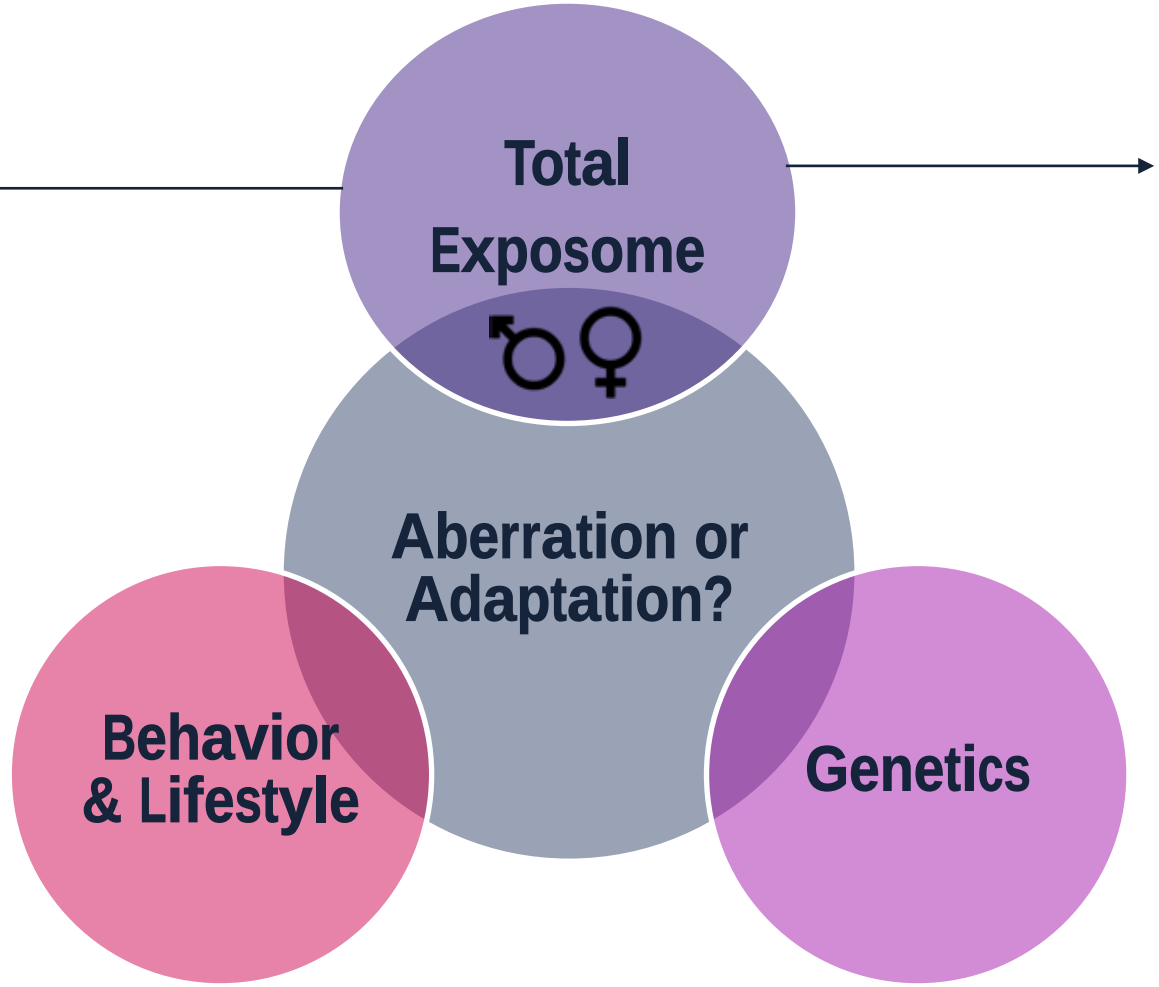
Paternal, maternal preconception environments impact fertility, pregnancy, child health

Few studies able to examine this critical period of vulnerability such as pre and periconception

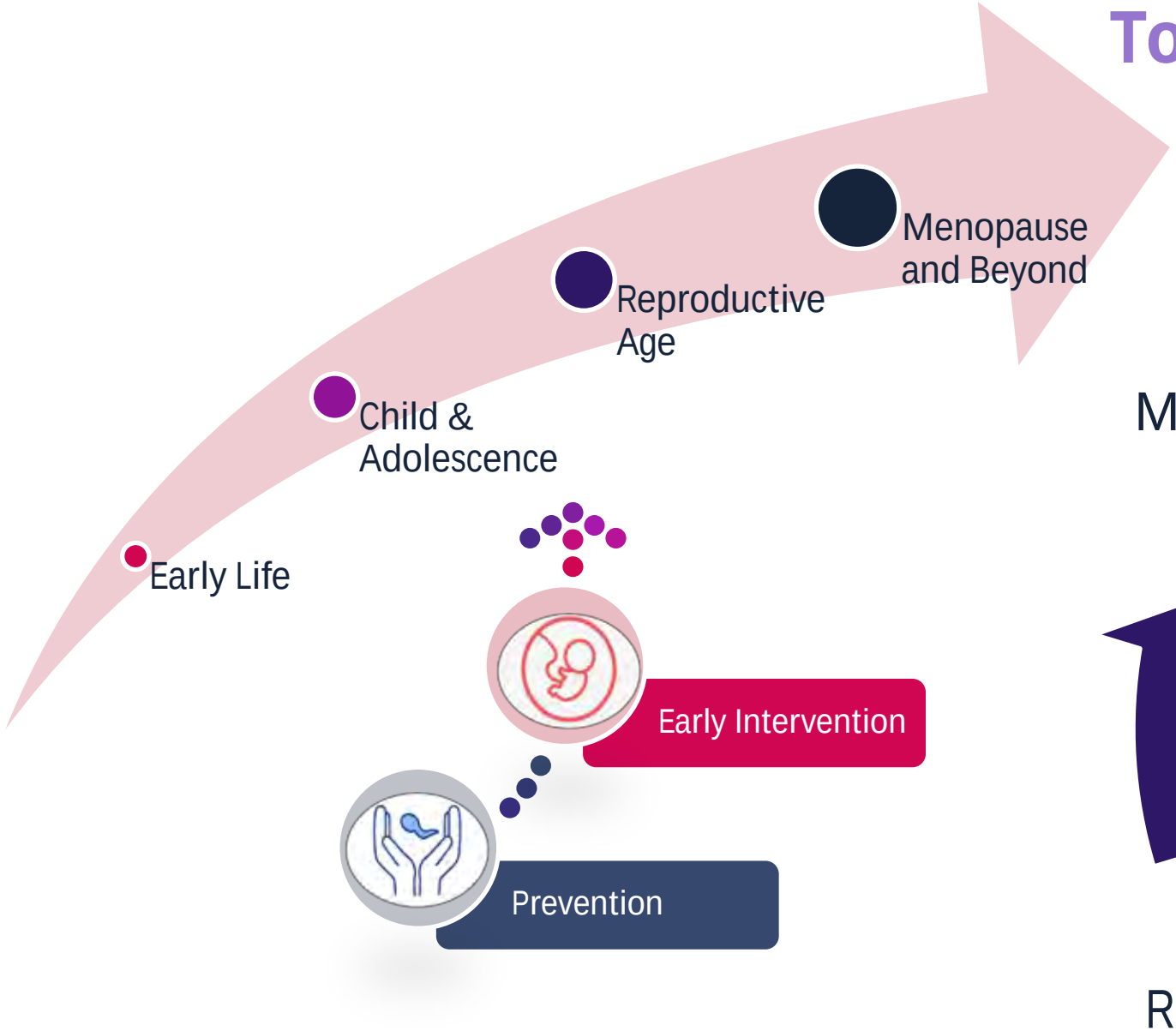
Reproductive Success?

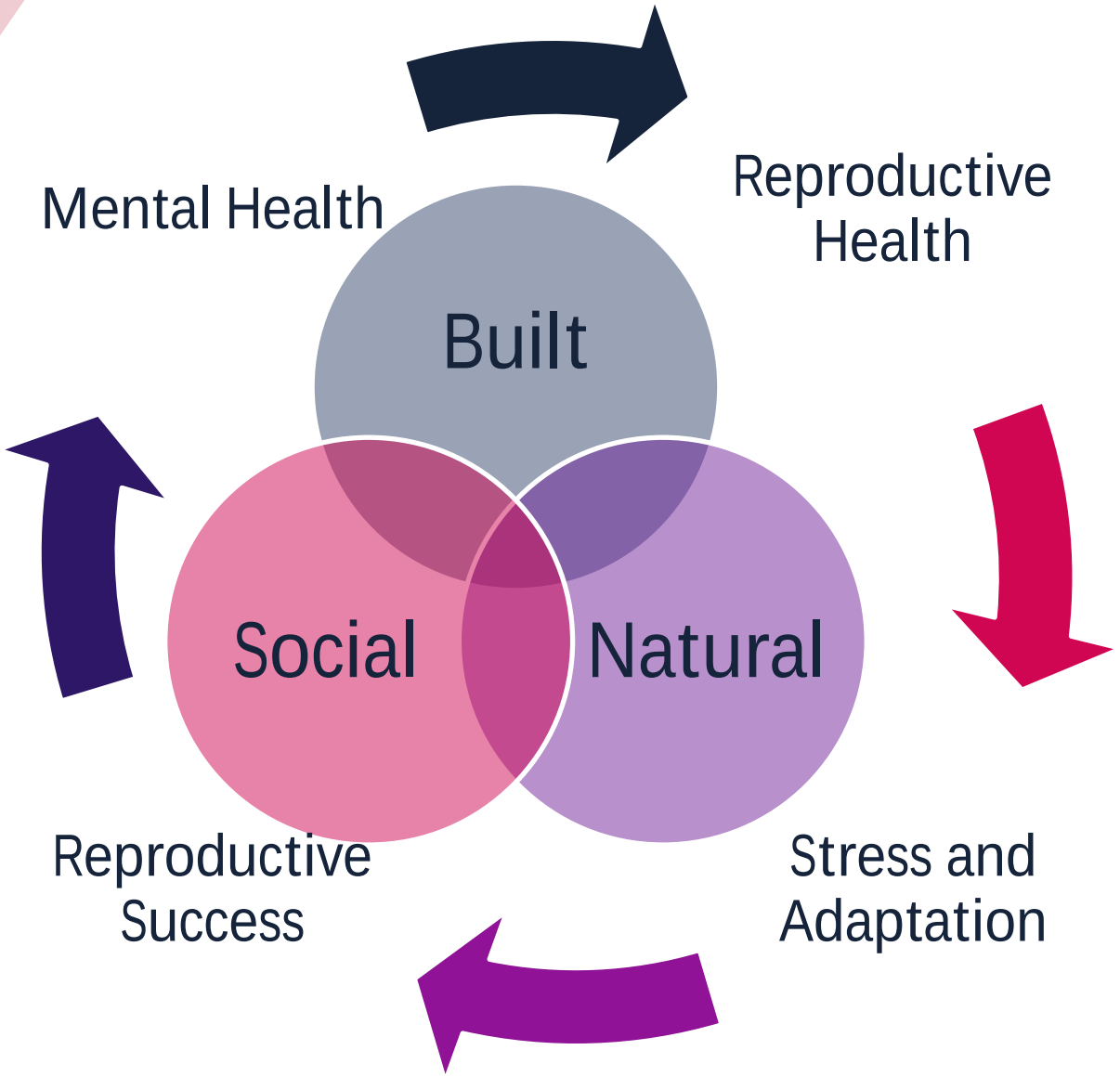
Social Environment

Natural and Built Environment

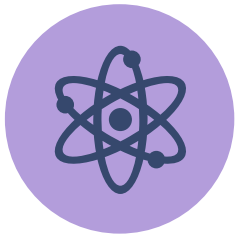


Towards an Integrated Model





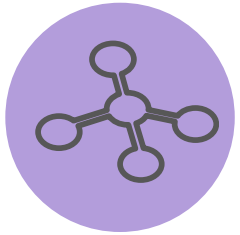
The Built Environment



EDCs

Endocrine Disrupting Chemicals (EDCs)

Exogenous chemicals that interfere with any aspect of endocrine system or hormonal action



PHTHALATES

High Molecular Weight
Medical devices, toys

Low Molecular Weight
Paints, adhesives
Personal care products

BPA

Plastic bottles
Food packaging
Toys

PFAS

Water contamination
Meat/dairy
Food contact material

MIXTURES

Beyond a single-chemical problem, real word exposure scenarios are much more complex

Environment International
Volume 151, June 2021, 106440

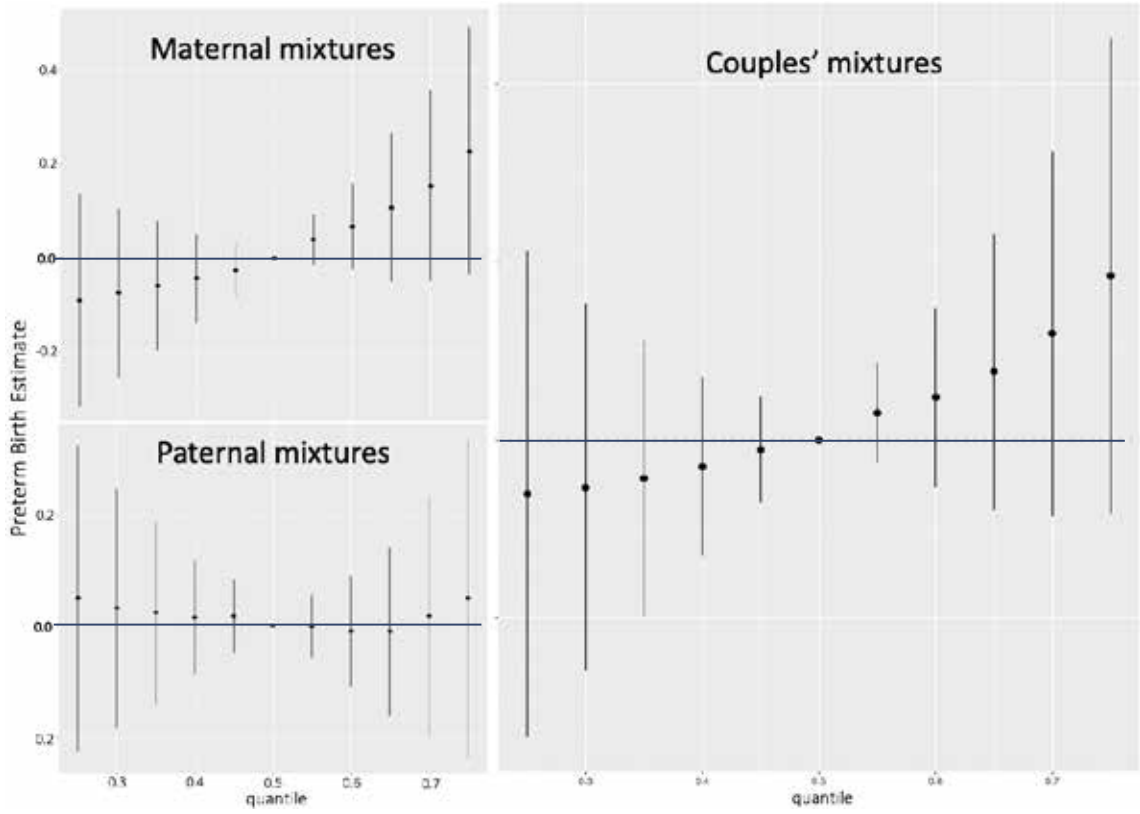
Parental preconception exposure to phenol and phthalate mixtures and the risk of preterm birth

Yu Zhang [a c], Vicente Mustieles [b c d], Paige L. Williams [c f], Blair J. Wylie [g], Irene Souter [h i], Antonia M. Calafat [j], Melina Demokritou [a], Alexandria Lee [e], Stylianos Vagios [h i], Russ Hauser [a e], Carmen Messerlian [a e h i]

- Paternal preconception DEHP and maternal BPA à higher preterm birth, holding all other biomarker at median concentration

- Higher preterm birth across quantiles of maternal and couples' total mixture concentrations

CUMULATIVE EFFECT OF TOTAL MIXTURE

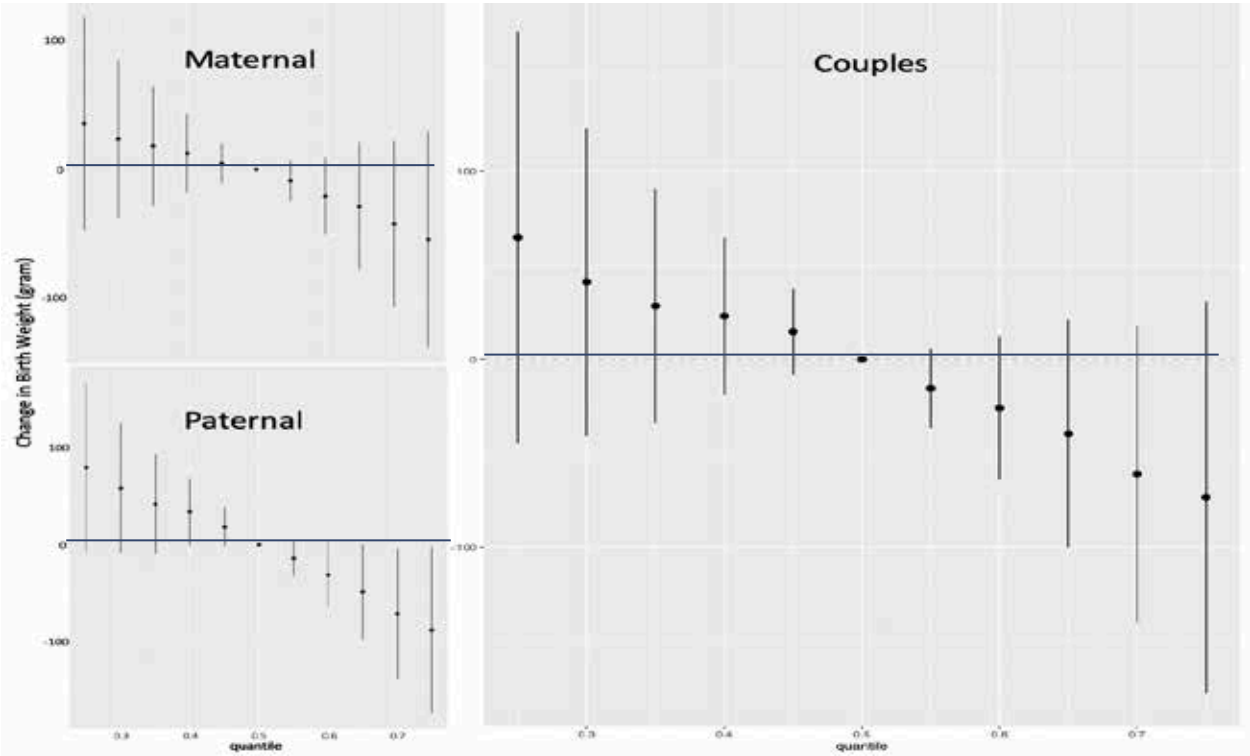


Increasing trend of **preterm birth** across quantiles of **maternal** and **couples**' total preconception mixture concentrations

Couples' Mixtures & Birthweight

- Paternal MBP and maternal preconception BPA à decreased birthweight, holding all other biomarkers at median concentration
- Lower birthweight across quantiles of maternal, paternal and couples' total mixture concentrations

CUMULATIVE EFFECT OF TOTAL MIXTURE



Decreasing trend of **birthweight** across quantiles of **maternal**, **paternal** and **couples**' total preconception mixture concentrations

PFAS and Human Health

- PFAS - found in the water we drink, the food we eat, the air we breath
- High production volume synthetic water and stain resistant chemicals
- Countless diverse commercial and consumer applications (non-stick pans, textiles, food packaging, water)
- Universally detected in general population worldwide
- Resist environmental degradation and then bioaccumulates in food-chain





Preconception PFAS and Reproduction (PREPARE) Study

Funded by:

NIEHS R01ES031657, 2020-2025

SEED PROGRAM
SCIENTIFIC EARLY LIFE ENVIRONMENTAL HEALTH & DEVELOPMENT PROGRAM

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

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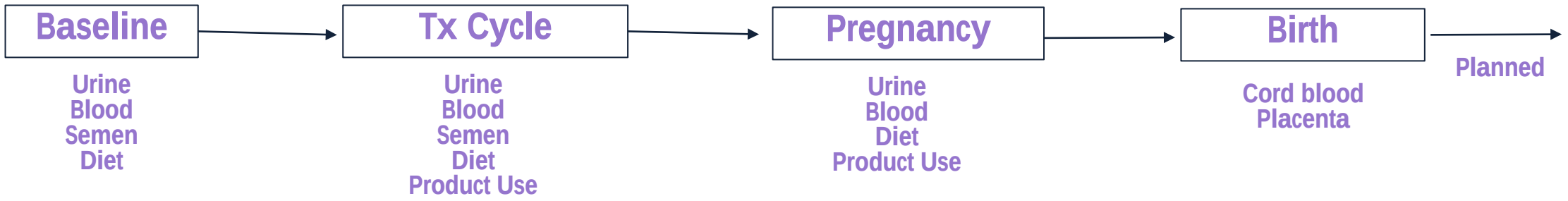
NIH NIEHS

The PREPARE Study Aims

Measure preconception serum PFAS concentrations among female and their male partners recruited from 2003 to 2019 in the EARTH Study and then the Prepare Study 2022-2025 at the Massachusetts General Hospital Fertility Center

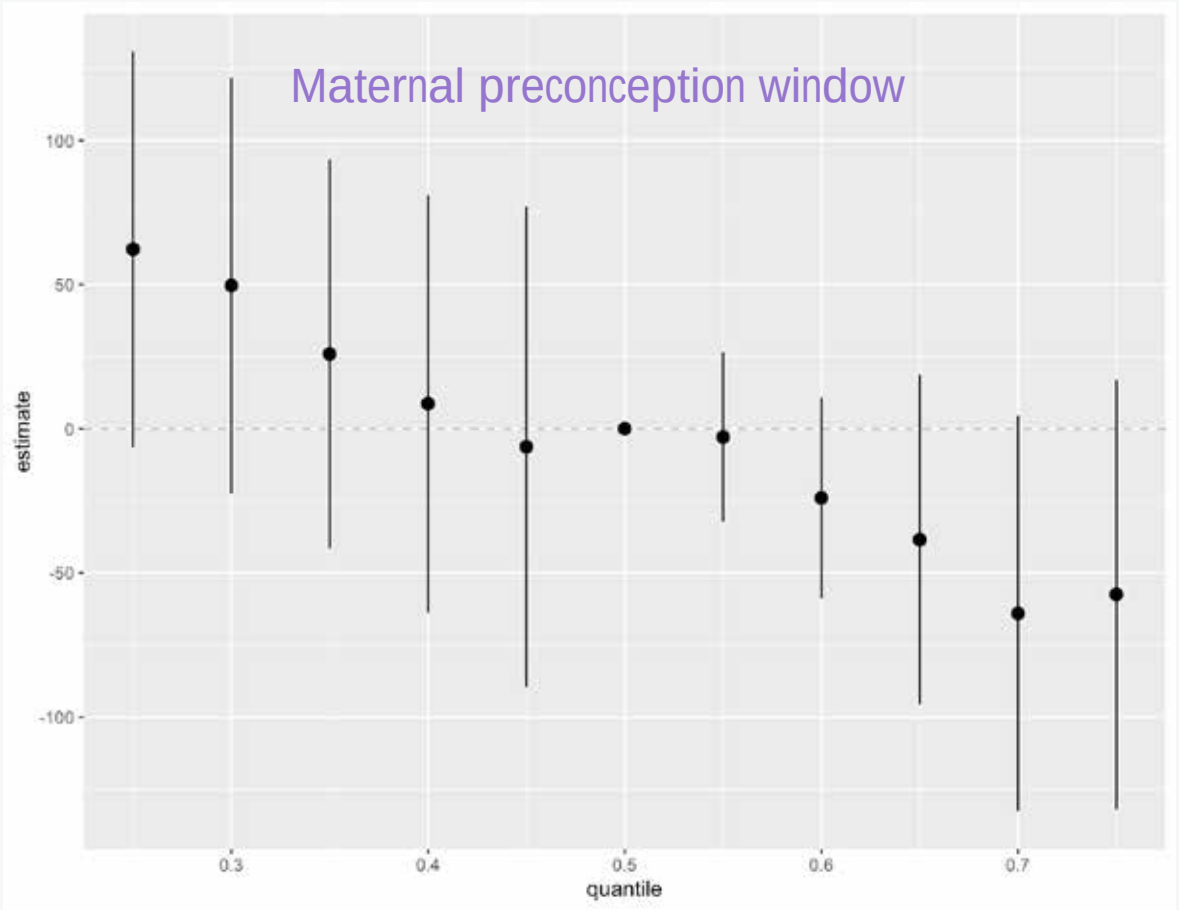


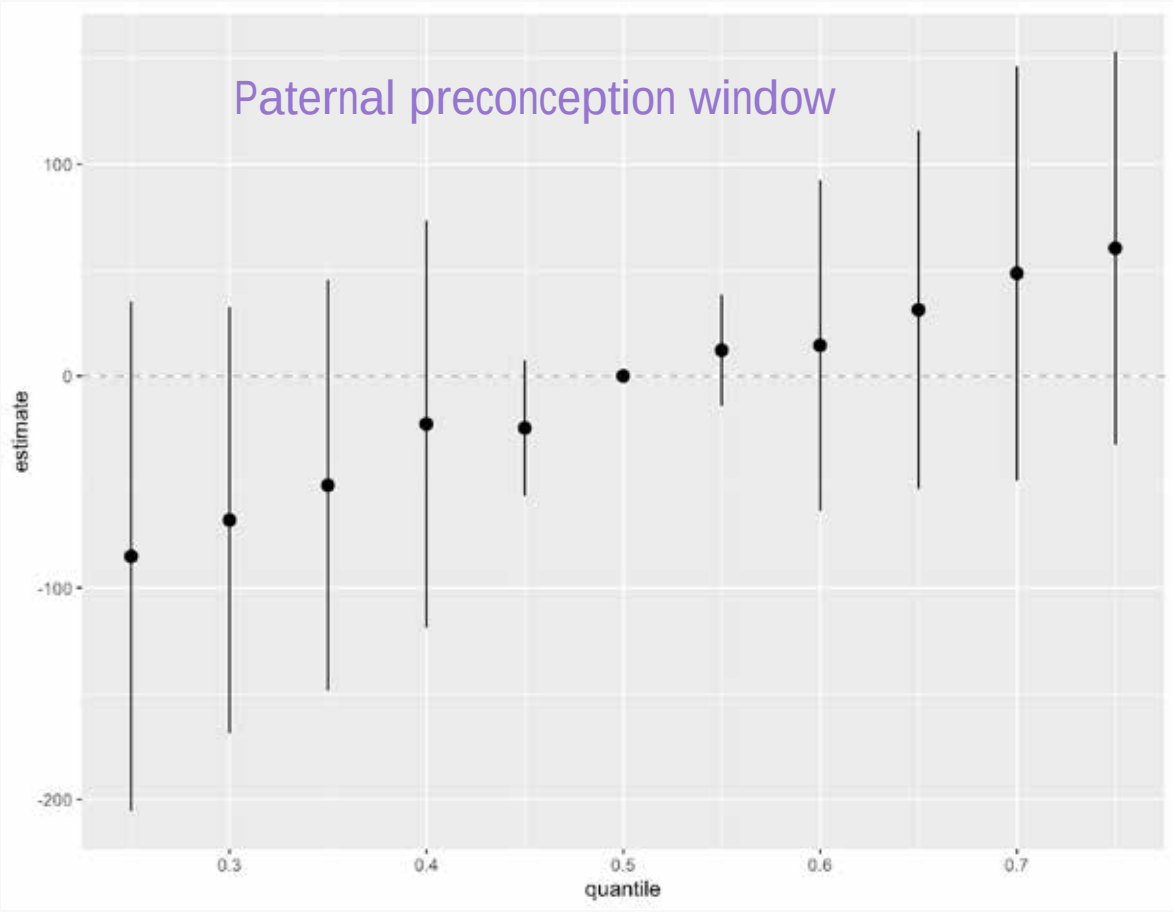
PFAS and Birth Weight

Maternal and paternal preconception PFAS concentrations and birthweight (g) among 312 singletons

PFAS	Maternal Beta (95% CI)	Paternal Beta (95% CI)
PFOA	-41.32 (-163.24, 80.61)	124.86 (-64.35, 314.06)
PFOS	**-161.44 (-268.31, -54.58)**	**147.81 (-7.9, 303.52)**
PFNA	-40.7 (-140.79, 59.38)	105.73 (-64.91, 276.36)
PFHxS	**-94.26 (-180.4, -8.11)**	**127.13 (-2.75, 257)**
PFDA	-46.93 (-161.62, 67.77)	41.65 (-136.92, 220.22)
PFUnDA	-55.44 (-140.01, 29.14)	10.7 (-116.01, 137.41)
Mixture	**-96.90 (-195.75, 1.96)**	80.31 (-66.42, 227.04)

Joint Effect of PFAS Mixture on Birth Weight





PFAS Concentrations and Thyroid Function in 287 Females

		Percent Change (95% CI)
Total Triiodothyronine (TT3)		
	PFOA	**-4.22 (-7.9, -0.39)**
	PFOS	-2.96 (-6.2, 0.39)
	PFHxS	-2.58 (-5.31, 0.23)
	PFNA	**-3.03 (-5.95, -0.01)**
	PFUnDA	**-4.04 (-6.51, -1.5)**
	PFDA	**-5.56 (-8.82, -2.17)**
	Mixture	**-4.45 (-7.15, -1.67)**
FT4/FT3		
	PFOA	1.22 (-1.36, 3.87)
	PFOS	0.58 (-1.65, 2.86)
	PFHxS	**1.16 (-0.71, 3.06)**
	PFNA	**2.22 (0.18, 4.29)**
	PFUnDA	**2.45 (0.71, 4.23)**
	PFDA	**3.2 (0.83, 5.62)**
	Mixture	**1.78 (-0.13, 3.73)**

PFAS & Nutrient Modifiers

Observational Study > Lancet Planet Health. 2023 Jun;7(6):e449-e458.
doi: 10.1016/S2542-5196(23)00088-8.

Folate concentrations and serum perfluoroalkyl and polyfluoroalkyl substance concentrations in adolescents and adults in the USA (National Health and Nutrition Examination Study 2003–16): an observational study

Yu Zhang [1], Vicente Mustieles [2], Yi-Xin Wang [3], Yang Sun [4], Juliana Agudelo [5], Zainab Bibi [6], Nicole Torres [6], Youssef Oulhote [7], Angela Slitt [5], Carmen Messerlian [8]

NHANES
2003 - 2016 cycles
2,802 Adolescents
9,159 Adults

Adults: Folate in Red Blood Cells (RBC) à PFAS

Adjusted % Change in Serum PFAS Concentration Per 2.7-fold Increase in RBC Folate

Biomarkers	Adjusted Percent Change (95%CI)	Adjusted (+diet) Percent Change (95%CI)
PFOA	-12.45% (-17.28%, -7.35%)	-11.18% (-16.36%, -5.68%)
PFOS	-25.30% (-29.67%, -20.65%)	-23.54% (-28.27%, -18.49%)
PFHxS	-21.65% (-26.19%, -16.82%)	-20.47% (-25.35%, -15.27%)
PFNA	-11.70% (-17.32%, -5.70%)	-9.50% (-15.54%, -3.02%)

Adolescents: Folate in Red Blood Cells (RBC) à PFAS

Adjusted % Change Serum PFAS Concentration Per 2.7-fold Increase in RBC Folate

Biomarkers	Adjusted Percent Change (95%CI)	Adjusted (+diet) Percent Change (95%CI)
PFOA	-7.34% (-16.57%, 2.91%)	-6.51% (-16.49%, 4.67%)
PFOS	-24.36% (-33.21%, -14.34%)	-25.14% (-34.18%, -14.86%)
PFHxS	-13.00% (-21.87%, -3.12%)	-14.68% (-23.51%, -4.84%)
PFNA	-12.29% (-26.12%, 4.12%)	-11.14% (-26.01%, 6.72%)

ELSEVIER

Environment International

Volume 164, June 2022, 107239

Full length article

Association between serum per- and polyfluoroalkyl substances concentrations and common cold among children and adolescents in the United States

Yu Zhang [a] ✉, Vicente Mustieles [b, c, d], Yang Sun [a, e], Youssef Oulhote [f], Yi-Xin Wang [g], Carmen Messerlian [a, c, h]

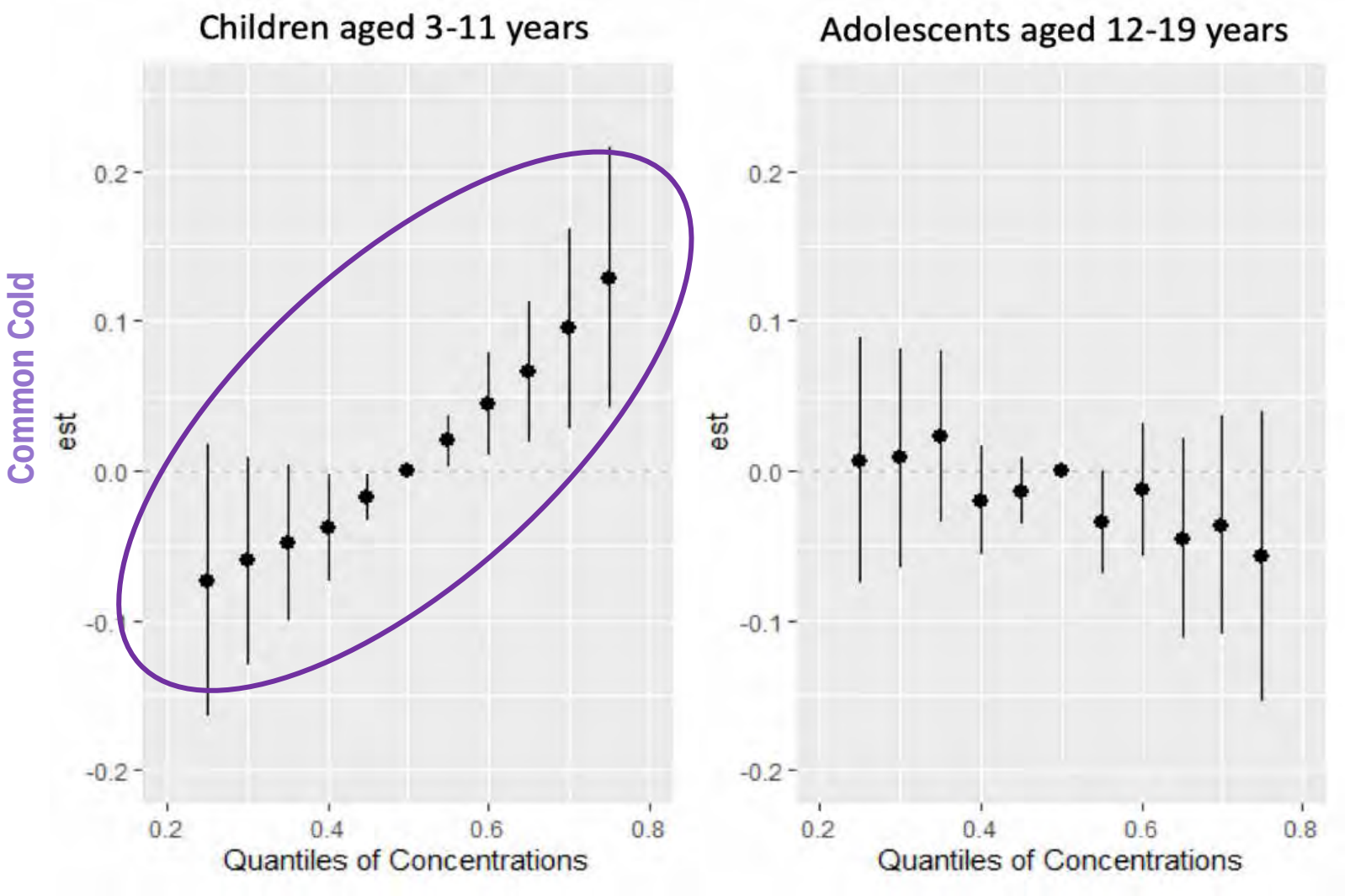
PFAS and Children's Health

NHANES

517 children 3–11 years, 2013–2014 cycles

2732 adolescents 12–19 years, 2003–2016 cycles

Change in common cold estimate per 5th percentile increase or decrease in the total PFAS mixture concentrations compared with the median total mixture concentration



PFAS and Folate in Project Viva

Early Pregnancy Plasma PFAS Concentrations and Birthweight, Stratifying By Folate Groups

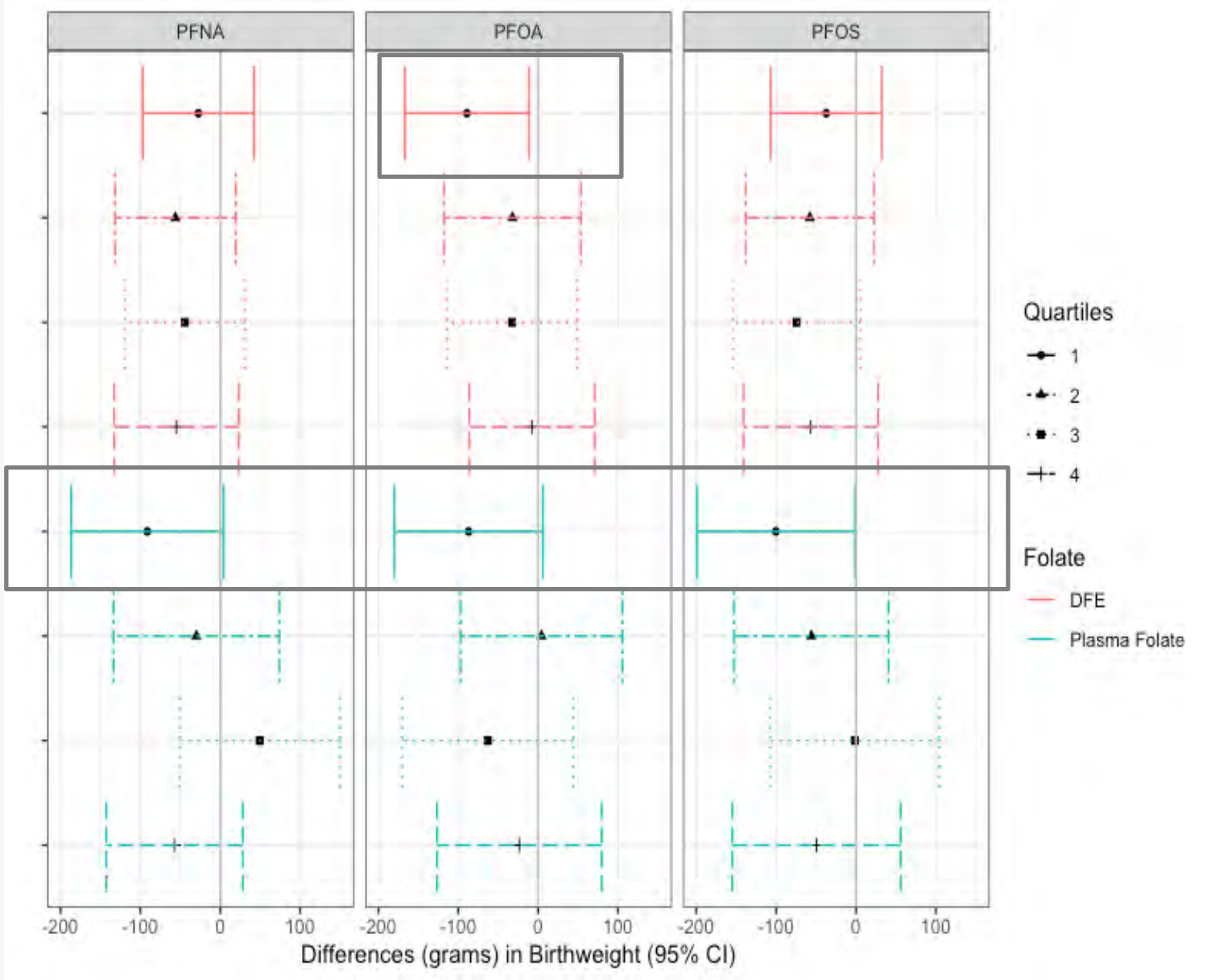
JAMA Netw Open. 2023 May 1;6(5):e2314934. doi: 10.1001/jamanetworkopen.2023.14934.

Association of Early Pregnancy Perfluoroalkyl and Polyfluoroalkyl Substance Exposure With Birth Outcomes

Yu Zhang [1], Vicente Mustieles [2], Qi Sun [3 4 5 6], Brent Coull [1 7], Thomas McElrath [5 6 8], Sheryl L Rifas-Shiman [9], Leah Martin [1], Yang Sun [1 6], Yi-Xin Wang [1 3], Emily Oken [3 9], Andres Cardenas [10], Carmen Messerlian [1 6 11]

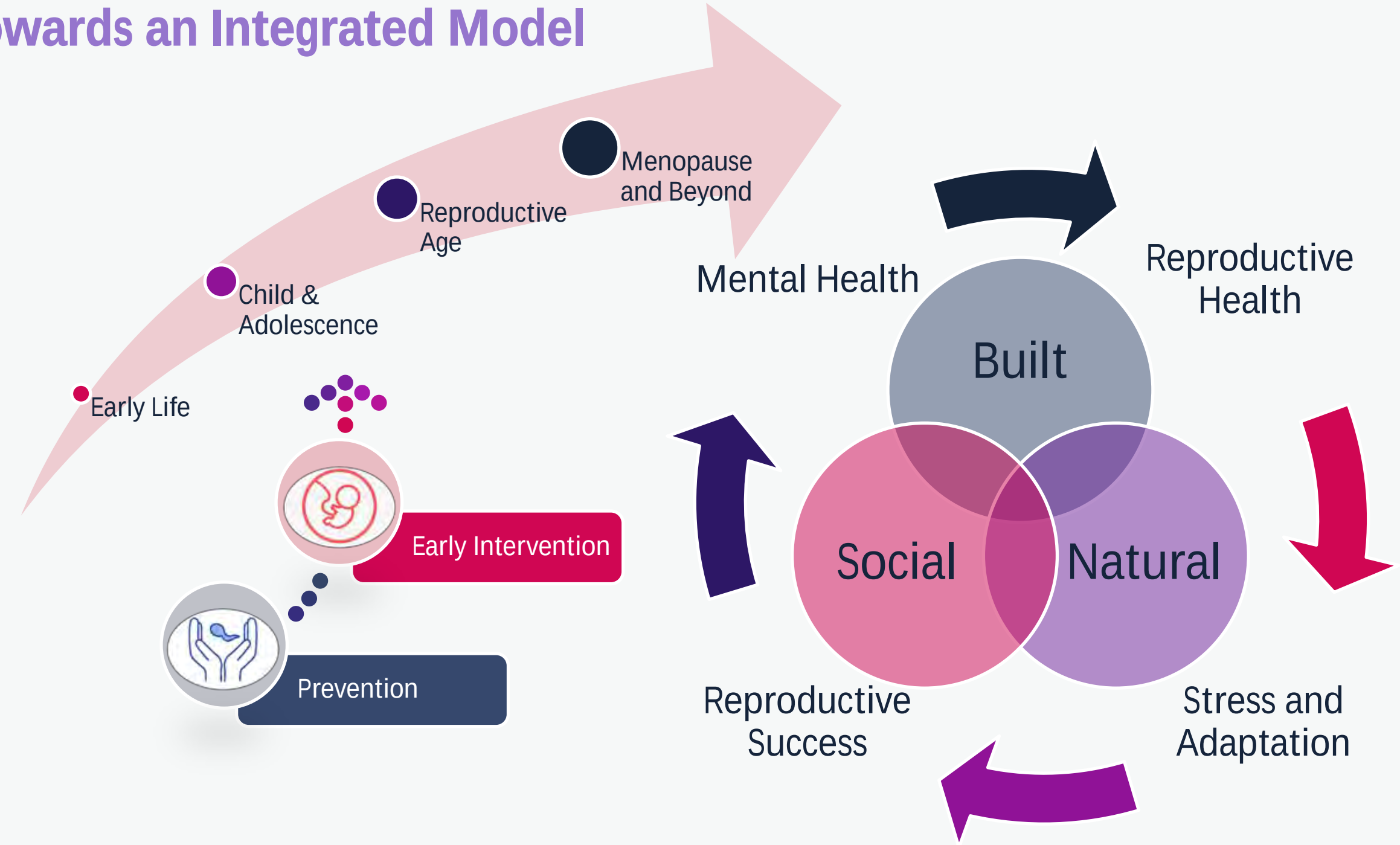
Affiliations + expand

PMID: 37256622 PMCID: PMC10233420 DOI: 10.1001/jamanetworkopen.2023.14934



- **PFOA - lower birthweight only in the lowest quartile group of dietary folate equivalent (DFE) intake**
- **PFNA, PFOA, PFOS - lower birthweight only in the lowest quartile group of plasma folate concentration**

Towards an Integrated Model



The Natural Environment

WATER

Disinfection by Products (DBP)

Municipal water

Swimming pools

Inhalation, dermal, ingestion

AIR

Ambient Air Pollutants

Nitrous Oxide (N02)

PM2.5

Ozone (O3)

DBPs and Human Health

NHANES

Xiaogan DBP Study

All Cause Mortality (published)

Oxidative Stress (published)

Birth Outcomes (published)

Neurodevelopment (published)

Fetal Growth (published)

Asthma, Children/Adolescents (published)

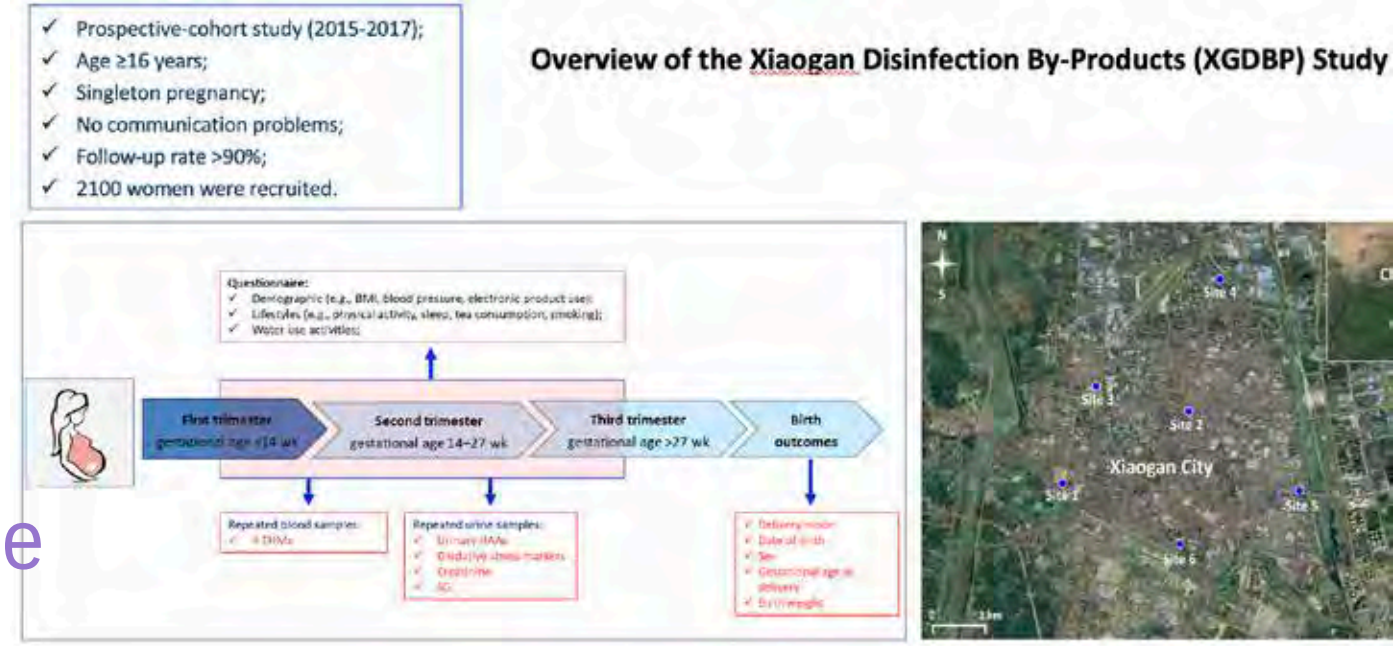
Thyroid Function (published)

Lung Function (published)

Allergic Sensitization (published)

Disinfection By Products (DBP) and Birth Outcomes

- Oxidative Stress
- Birthweight
- Fetal Weight
- Small for Gestational Age (SGA)



Xiaogan DBP Study

Windows of Vulnerability

ehp Environmental Health Perspectives

HOME ISSUE IN PROGRESS ARCHIVES COLLECTIONS AUTHORS REVIEWERS ABOUT

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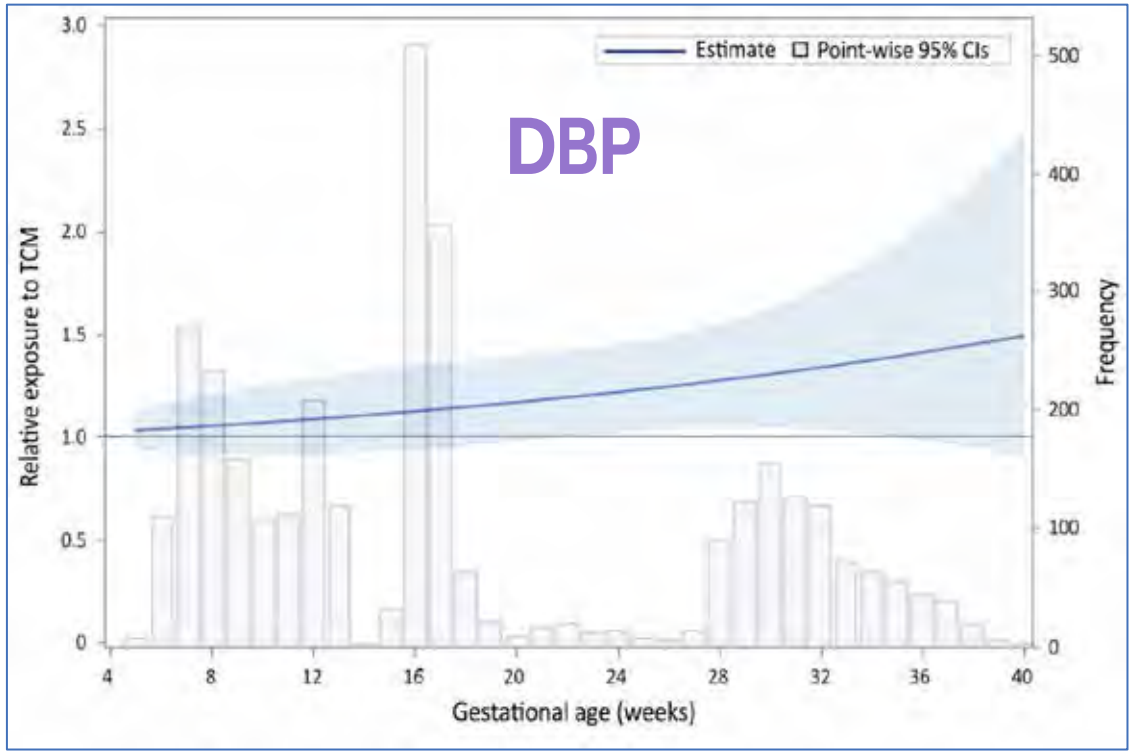
Vol. 128, No. 10 | Research

Trimester-Specific Blood Trihalomethane and Urinary Haloacetic Acid Concentrations and Adverse Birth Outcomes: Identifying Windows of Vulnerability during Pregnancy

Yang Sun, Yi-Xin Wang, Chong Liu, Ying-Jun Chen, Wen-Qing Lu, and Carmen Messerlian

Published: 7 October 2020 CID: 107001 https://doi.org/10.1289/EHP7195



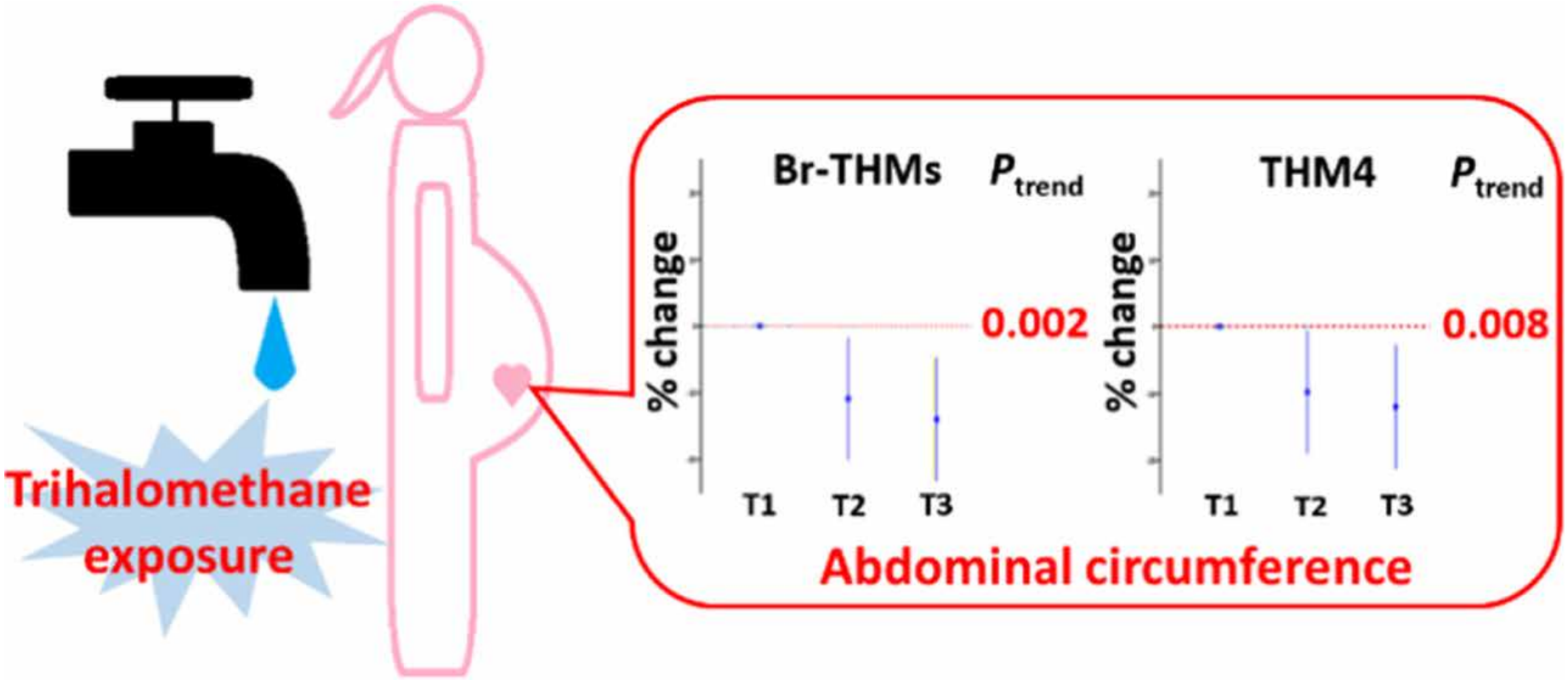
Relative exposure to TCM concentrations across gestational weeks, comparing SGA with non-SGA births

DBP and Fetal Growth

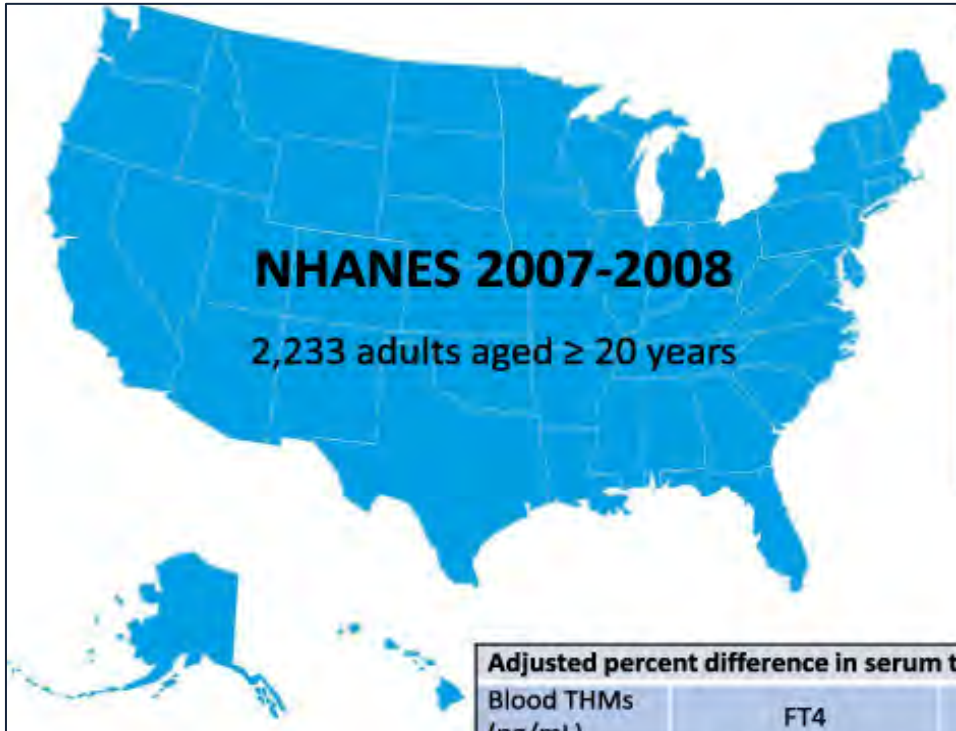
> Environ Sci Technol. 2021 Dec 7;55(23):16011-16022. doi: 10.1021/acs.est.1c04926. Epub 2021 Nov 23.

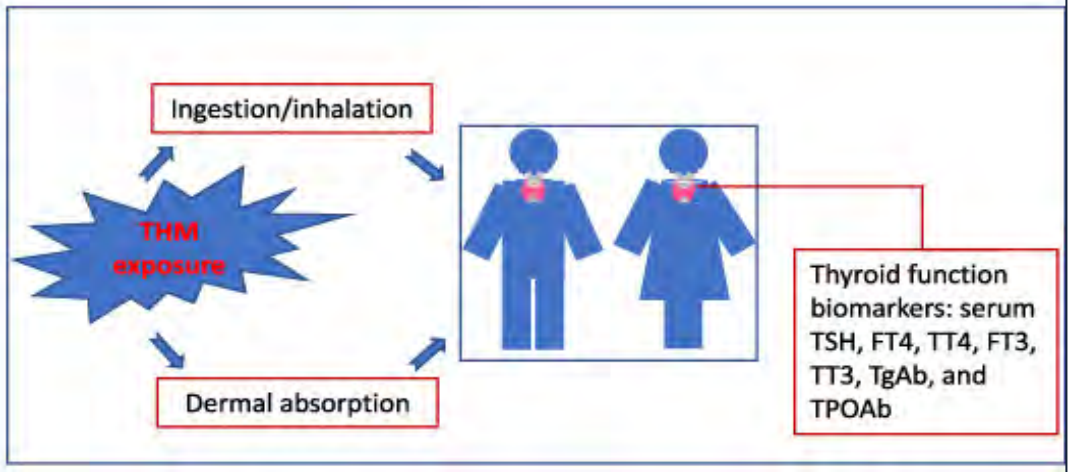
Prenatal Exposure to Disinfection Byproducts and Intrauterine Growth in a Chinese Cohort

Chong Liu [1 2], Yang Sun [3 4], Vicente Mustieles [5 6], Ying-Jun Chen [7], Li-Li Huang [8], Yan-Ling Deng [1 2], Yi-Xin Wang [9], Wen-Qing Lu [1 2], Carmen Messerlian [3 4]



DBP and Thyroid Function





Adjusted percent difference in serum thyroid function measures in relation to blood THM concentrations

Blood THMs (pg/mL)	FT4	TT3	FT4/FT3	TT4/TT3	FT3/TT3
TCM	**3.24 (1.29, 5.19)***	0.72 (-2.45, 3.93)	**3.05 (0.45, 5.68)***	1.16 (-2.87,5.25)	-0.54 (-3.44, 2.39)
BDCM	**2.65 (0.32, 5.01)***	-1.92 (-5.46, 1.67)	2.65 (-1.03, 6.38)	**4.26 (0.21, 8.39)***	1.91 (-1.39, 5.26)
DBCM	0.92 (-2.96, 4.86)	**-4.31 (-7.42, -1.16)***	1.21 (-3.47, 5.99)	**4.17 (0.83, 7.57)***	**4.04 (1.27, 6.85)***
Br-THMs	1.25 (-2.23, 4.78)	**-4.80 (-7.71, -1.85)***	2.08 (-2.36 ,6.60)	**5.44 (1.83, 9.11)***	**4.00 (0.91, 7.14)***
TTHMs	**3.16 (0.58, 5.77)***	-1.66 (-4.49, 1.62)	3.28 (-0.17, 6.78)	3.20 (-1.17, 7.65)	1.52 (-1.49, 4.57)

*P < 0.05.

Environmental Exposures & Cerebral Palsy (CP)

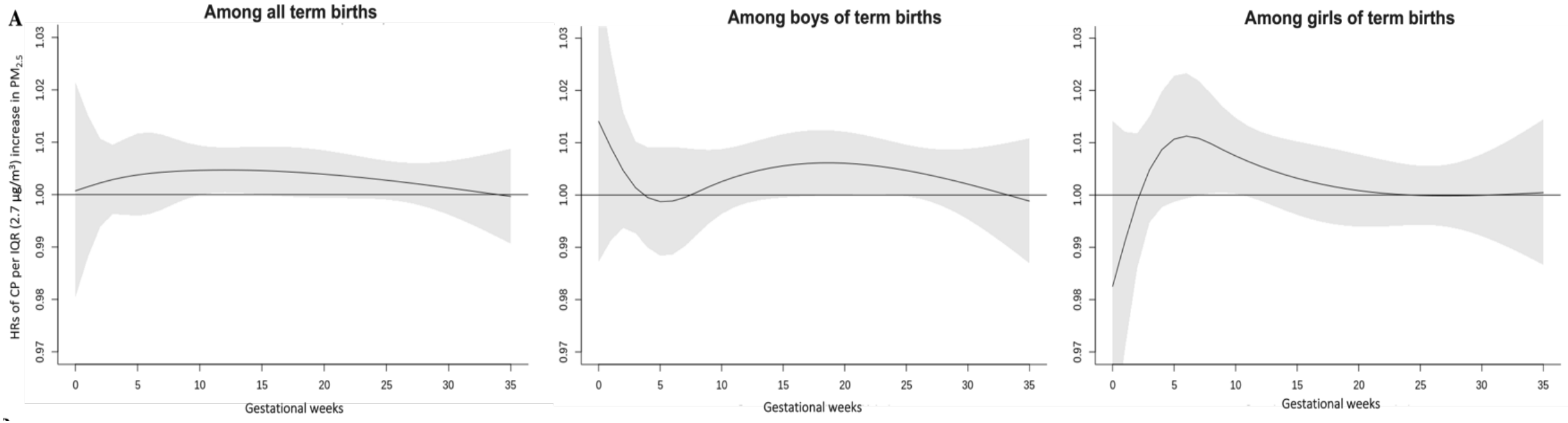
Y Hu , Y Zhang , R Talarico , X Qiu , J Schwartz, DB Fell, M Oskoui, E Lavigne, C Messerlian

Prenatal Exposure to Ambient Air pollution and Cerebral Palsy (CP) in Ontario, Canada Submitted, JAMA

IC/ES Data Discovery Better Health

Prenatal Exposure to Ambient Air Pollution & CP

Overall and sex-specific HRs of CP among term births



- >1.6 million singleton births in Ontario
- Multipollutant Cox proportional hazards model with distributed non-linear lag – weekly AP
- $PM_{2.5}$ exposure during pregnancy increased CP risk by ~10%

Prenatal Exposure to Ambient Air Pollution & Cerebral Palsy

Overall and sex-specific HRs of CPs among term births

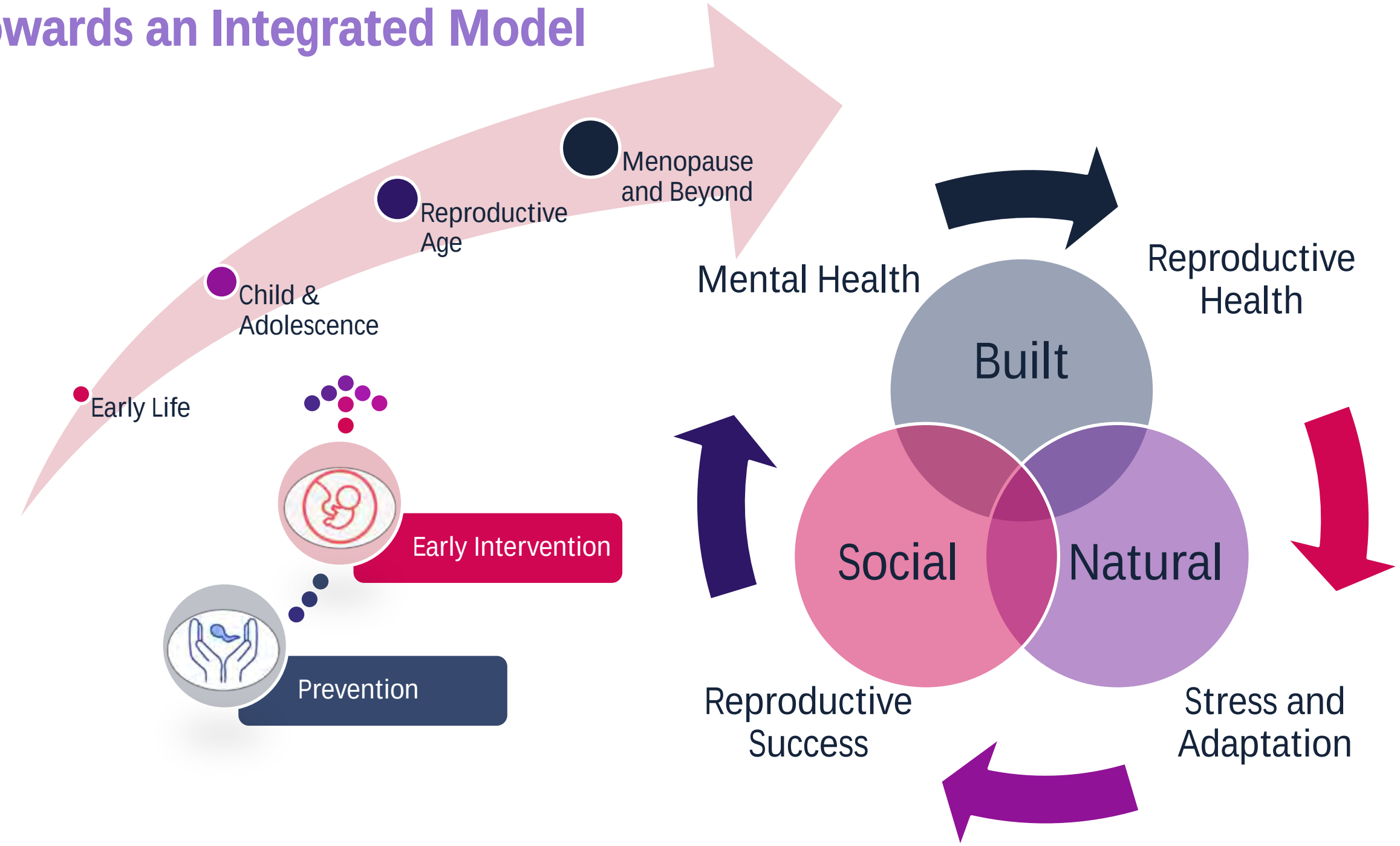
Pollutant	HRs (95% CI)[a]			p-value[b]
	All	Males	Females	
$PM_{2.5}$ (per 2.7ug/m^3)	1.11 (1.03, 1.20)	1.14 (1.02, 1.26)	1.06 (0.96, 1.22)	0.8463
NO_2 (per 10ppb)	0.93 (0.84, 1.02)	0.95 (0.83, 1.08)	0.90 (0.77, 1.04)	0.2207
O_3 (per 7ppb)	0.97 (0.90, 1.04)	0.93 (0.85, 1.02)	1.02 (0.92, 1.15)	0.7155

[a] The lengths of the exposure period during pregnancy for calculation of cumulative HRs are week 0-week 36 for the term births

[b] The p-values of effect modification by sex was derived by adding an interaction term between child's sex and each air pollutant and conducting Likelihood Ratio test with the primary models separately

We found positive associations between exposures to $PM_{2.5}$ over gestational weeks 0 to 33 and increased CP risk among term births with the statistically higher risk between weeks 11 and 14

Towards an Integrated Model



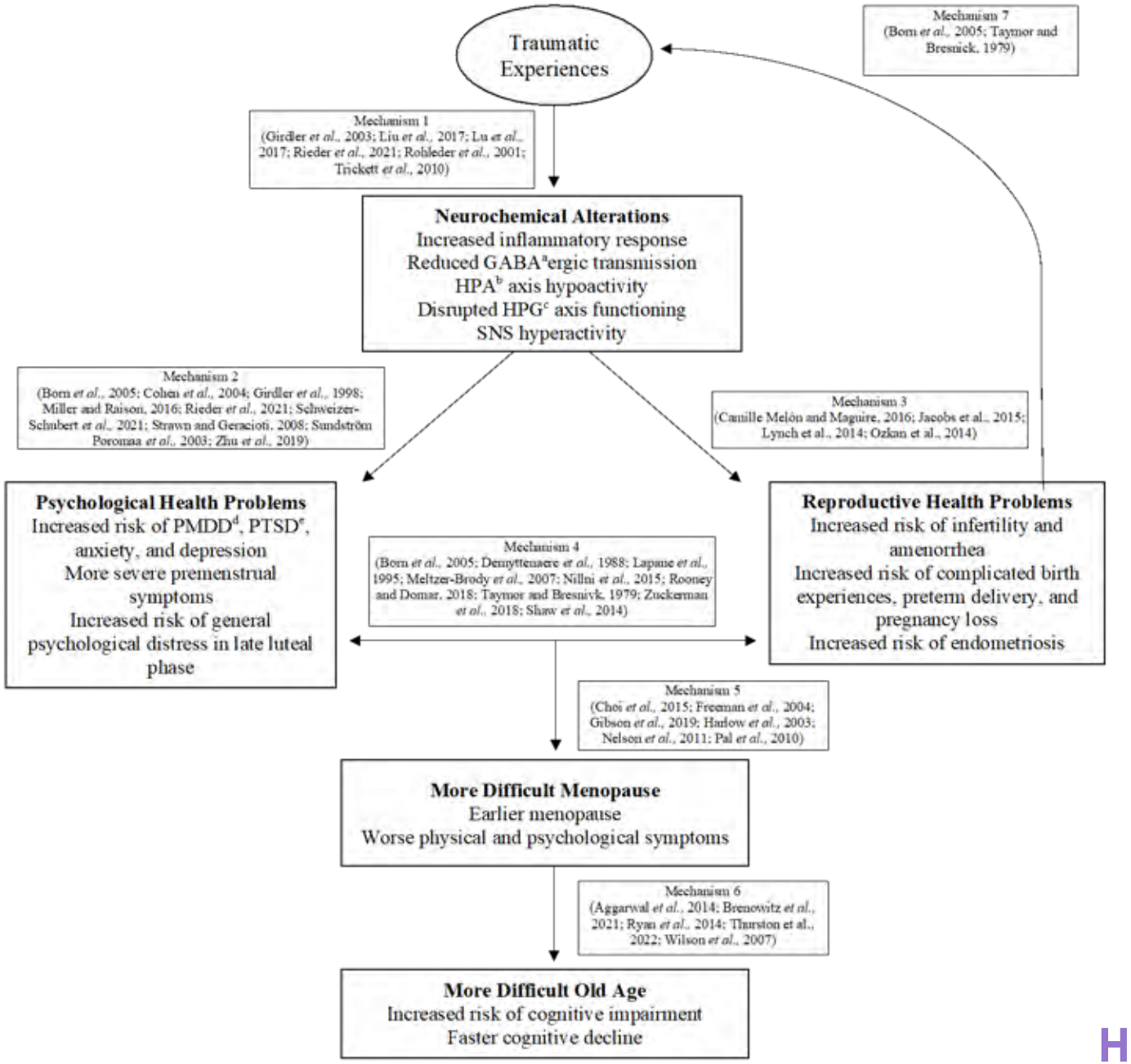
The Social Environment

Early Life Stress

Trauma
Stressful Life Experience
Child Maltreatment
Familial Dysfunction

Sexual and Reproductive Exposure

Age at Menarche
Sexual Experience
Fertility
Pregnancy
Post Partum
Menopause



Trauma and Reproductive Health Across Life

Hillcoat & Messerlian, Human Reproduction

The Preconception Intervention Program for Healthy Reproduction (PIPER) Project

Funded by:

Harvard Scientific Advancement Award (PI: Messerlian)

R01 NIEHS, to be resubmitted (PI: Messerlian)

SEED PROGRAM
SCIENTIFIC EARLY LIFE ENVIRONMENTAL HEALTH & DEVELOPMENT PROGRAM

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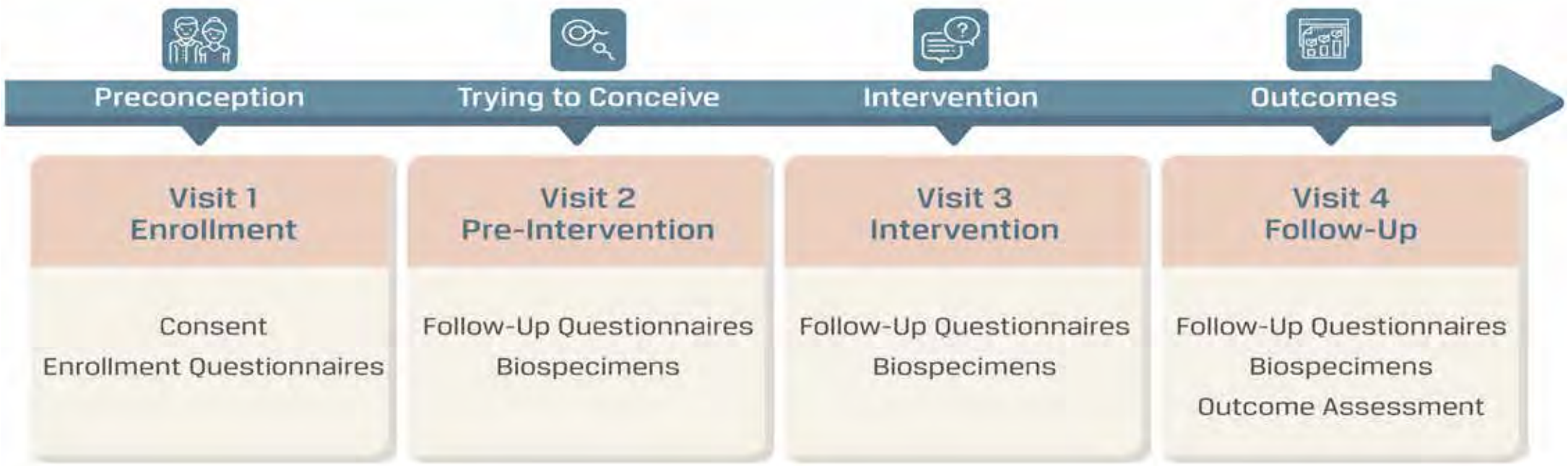
NIH NIEHS

The PIPER Project



Implement a randomized controlled trial design to examine the impact of our intervention on fertilization, implantation, and pregnancy loss

The PIPER Intervention

Tips to Reduce Your Exposure

Food & Drinks

Chemicals may come out of plastic containers into your food and drinks

Use glass or stainless steel containers for food and drinks

Avoid microwaving food in plastic containers, instead use glass or ceramic containers

Brew coffee in a glass or stainless steel French press instead of a plastic coffee maker

Choose organic produce, meat, and dairy when possible

- Choose lower % fat, higher % lean meats
- Look for the USDA organic label
- Look for 5 digit PLU labels that start with the number 9—these indicate the produce is organic

Choose safer plastics:

Plastics to avoid:

Cook more meals at home with fresh ingredients

Studies have shown that people who eat more meals prepared outside the home have higher levels of BPA

Choose fresh or frozen instead of canned food or drinks

BPA and phthalates can migrate from the linings of cans and plastic packaging into food and drinks

Replace plastic cooking utensils with wood or stainless steel

Personal Care Products & Cosmetics

Seek products that say "fragrance-free" on the label

Avoid buying personal care products with the words "fragrance" or "parfum" on the label

Avoid toothpaste, deodorant, & other products containing triclosan or triclocarban

Avoid products that say "antibacterial"

Avoid chemical UV filters in daily moisturizers and sunscreens

Choose shade, hats, and tightly woven clothing instead of sunscreen when you can

Choose safer period products

Tampons, pads, liners - Look for:

- 100% organic cotton or natural materials
- unscented and fragrance-free
- plastic-free packaging
- plastic-free applicator or tampon without applicator

Menstrual cups - Look for:

- 100% medical-grade silicone
- non-toxic cleaning methods

Look for plant-based products

The USDA Organic label or "Made with organic ingredients" indicates products mostly made of plants

Avoid nail polish & nail polish remover

Choose mineral instead of chemical sunscreens

- ✗ Benzophenone
- ✗ Oxybenzone
- ✗ Octinoxate
- ✗ Octyl methoxycinnamate
- ✓ Zinc oxide
- ✓ Titanium dioxide

Avoid cosmetics and personal care products with parabens listed on the label

Common names for these chemicals include butyl paraben, ethyl paraben, methyl paraben, and propyl paraben

Home & Cleaning

Chemicals in plastic end up in your dust, Keep dust levels low

Wipe surfaces with a damp cloth and use a vacuum with a HEPA (high-efficiency particulate air) filter

Clean with plain water, baking soda, vinegar, or castile soap when possible

Open windows or use vents when using products that have strong smells

Don't use fabric softeners or dryer sheets

try baking soda, vinegar, or dryer balls to soften clothes if needed

Get rid of mothballs

Avoid products with fragrances

Air fresheners
Cleaning products
Soaps
Dryer sheets
Laundry detergents & fabric softeners
Candles

Use nontoxic alternatives to toilet bowl deodorizers,

such as lemon juice, borax, baking soda, or white vinegar

Avoid tracking pollutants into your home

Place rugs in doorways and take off your outdoor shoes at the door

Use the Label to Find Safer Products: Cleaners & Laundry Detergents

Look for	Avoid
• Fragrance-free • Plant-based, "Made with organic ingredients" • Safer Choice logo	• "Poison", "danger", "caution", or "warning" on the label • Products advertised as **antibacterial, antimicrobial,** or **stain-protecting**

Educational Resources

EDCs & Reproductive Health

Understanding everyday toxicants and how you can minimize your exposure

Additional Resources

Learn more about the chemicals in your everyday products and environment:

The Environmental Working Group: www.ewg.org

Explore our website: www.seed-program.org

Contact & Follow us: SEED@hsph.harvard.edu (Twitter and Instagram) @drmesserlian

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How can I minimize my EDC exposure?

CHEMICAL FREE

- Wash your hands frequently, especially before meals
- Rinse produce thoroughly and buy organic when possible
- Avoid foods and beverages stored in plastic or canned containers
- Filter your water and use glass or metal storage containers
- Replace personal care and household products that have fragrance with safer products
- Look for phthalate-, paraben-, and chemical-free products
- Look for these labels:

100% FRAGRANCE FREE

EDCs

Endocrine-disrupting chemicals (EDCs) interrupt normal hormonal activity by mimicking, blocking, or altering hormones and changing the way that they function in the body.

EDCs include phthalates, phenols, per- and polyfluoroalkyl substances (PFAS), and other toxicants. Some EDCs are rapidly removed from the body, while others can remain in the body for a long time. Most people are exposed to multiple EDCs daily, allowing these chemicals to remain at harmful concentrations.

These chemicals damage your health

Current research suggests that EDCs lead to adverse health effects. These chemicals can:

- ✕ Alter reproductive health
- ✕ Reduce immune function
- ✕ Increase cancer risk
- ✕ Change metabolic function
- ✕ Decrease brain function

How do EDCs enter the body?

- Ingestion
- Inhalation
- Absorption

Where can EDCs be found?

- Personal care products, nail polish, and cosmetics
- Takeout containers, plastic packaging, canned foods and beverages, and plastic kitchen and storage items
- Unfiltered water sources and processed drinks
- Furniture, electronics, cleaning products, candles, fresheners, and household dust
- Cigarette smoke, e-cigarettes, and other smoking devices

Advancing the Field

- Focus on Prevention and Early Intervention
- Integration of Built, Natural, and Social Environments
- Holistic Reproductive Health across the Lifecourse, including men in the process
- Moving to a multidimensional integrated framework of health and wellbeing through multimodal AI

ACKNOWLEDGEMENTS

Preconception PFAS Exposure and Reproduction (PREPARE) Study

R01ES031657 (PI: Messerlian)

NIEHS Program Officers

Antonia Calafat
Centers for Disease Control and Prevention

All SEED Program Team Members
Collaborators
Participants

Vincent Center for Reproductive Biology

Massachusetts General Hospital

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CDC

MGH 1811

Conclusions

- With increasing exposure to complex environments, we need more novel and multifaceted preventive strategies
- A holistic lens that considers built, natural, and social environments across the lifecourse is needed to solve for real world reproductive health issues focused on prevention
- Multimodal AI, interventions, and education are just the beginning translating evidence into prevention, personalized care, and improved outcomes

Maternal-Child Health Risks and Risk Reduction

Rita Strakovsky, Ph.D., R.D.

Associate Professor

Michigan State University

Exposure to non-persistent endocrine disrupting chemicals, maternal metabolic health, and roles of diet quality

Rita Strakovsky, Ph.D., R.D.
Associate Professor

Michigan State University
East Lansing, MI
strakovs@msu.edu

Office on Women's Health Endocrine Disrupting Chemicals and Women's Health Symposium. July 18 & 19, 2023.

OASH | Office on Women's Health

Maternal-Child Health Risks and Risk Reduction

Christine Langton, Ph.D.

Postdoctoral Fellow, Women's Health Group, Epidemiology Branch

National Institute of Environmental Health Sciences

PRE-RECORDING

Endocrine Disrupting Chemicals and Women's Health Symposium

Menopause and Uterine Fibroid Research

Christine R. Langton, Postdoctoral Fellow
Women's Health Group, Epidemiology Branch

National Institute of Environmental Health Sciences

Objectives of Presentation

- Early life exposures and later in life health
  - Menopause research
  - Uterine fibroid research

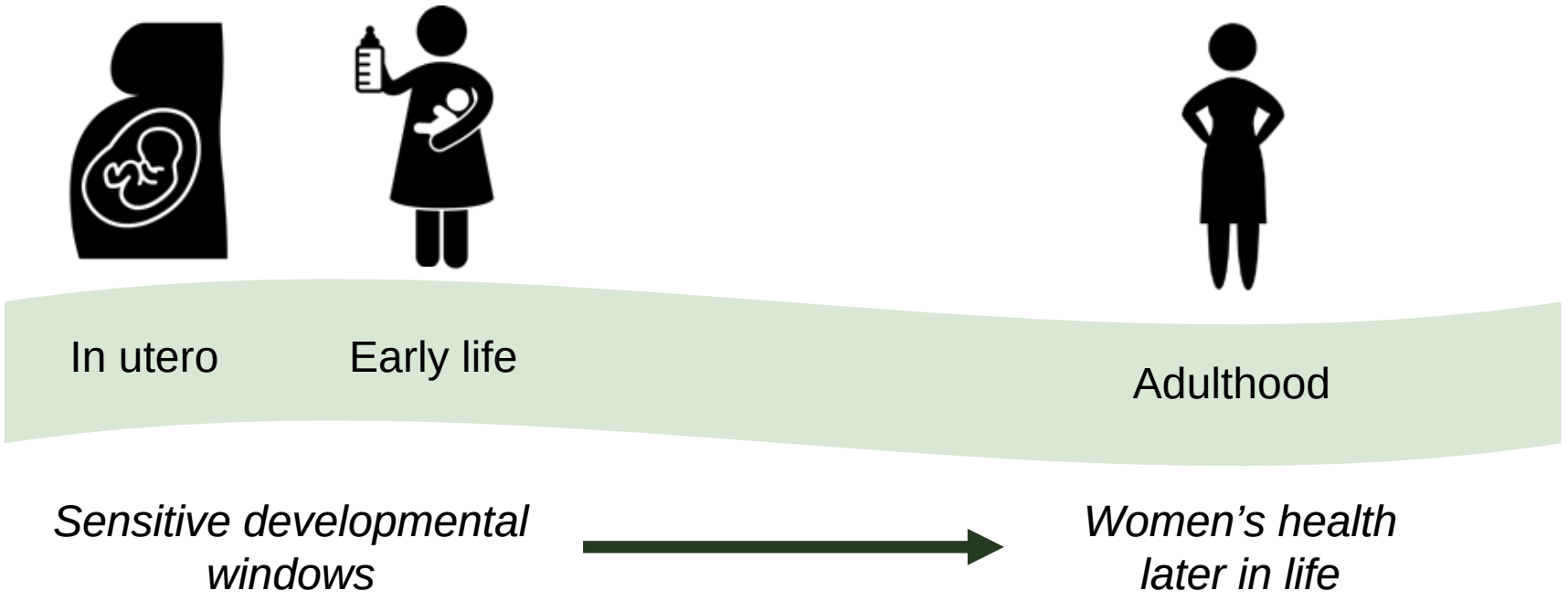
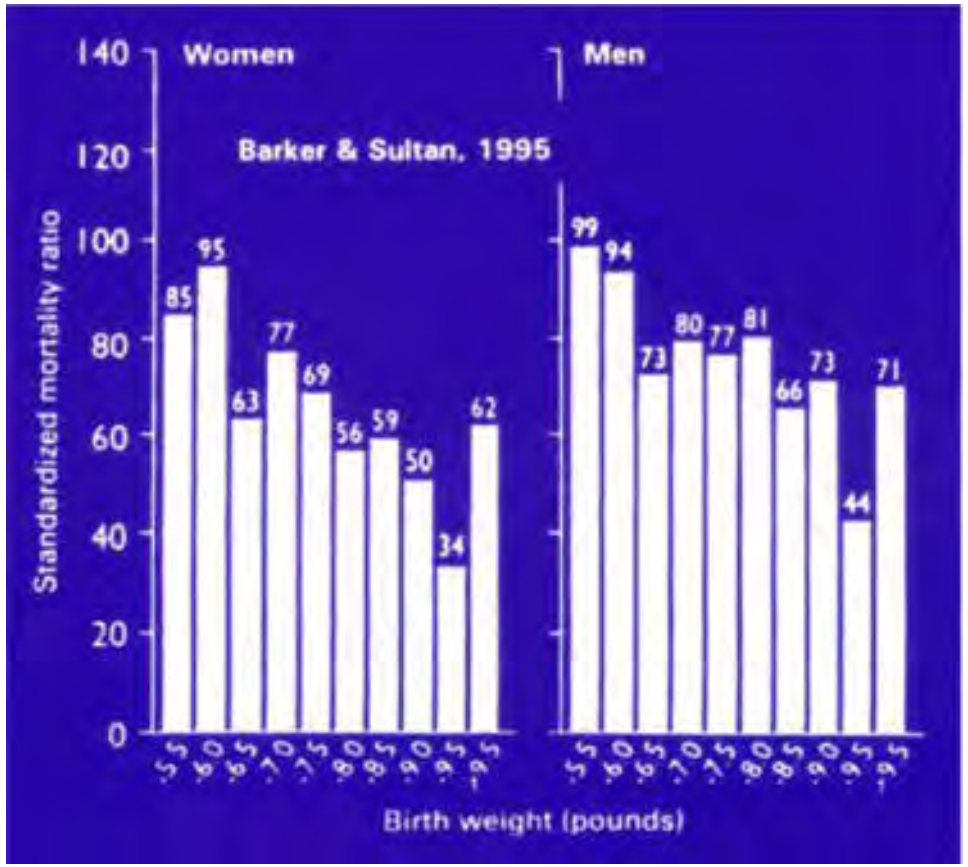


Image sources from Noun Project: Fetus, Lars Meiertoberens; Midwife, Gan Khoon Lay; Female aging, Marie Van den Broeck.

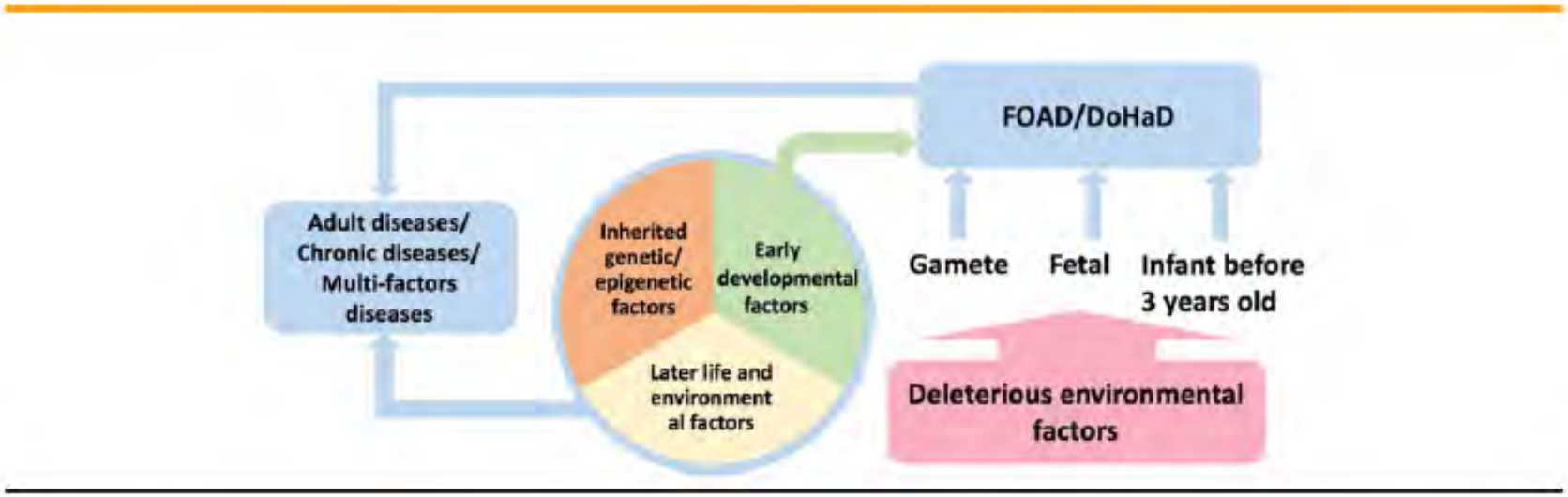
Fetal Origins of Adult Disease (FOAD)



- Developmental plasticity
- Beneficial in short-term to promote survival and reproduction
- Detrimental in long-term

Source: Calkins K, Devaskar SU. Fetal Origins of Adult Disease. *Curr Probl Pediatr Adolesc Health Care.* 2011;41(6):158-76.

Developmental Origins of Health and Disease (DoHaD)



- DoHaD linked to adult diseases
  - Type II diabetes, hypertension, CVD, cancer

Source: Li X et al. “Three Hits” Hypothesis for Developmental Origins of Health and Disease in View of Cardiovascular Abnormalities. *Birth Defects Res.* 2017;109:744-757.

In Utero Exposures and Menopause

American Journal of Epidemiology

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January 6, 2022

Original Contribution

Association of In Utero Exposures With Risk of Early Natural Menopause

Christine R. Langton*, Brian W. Whitcomb, Alexandra C. Purdue-Smithe, Lynnette L. Sievert, Susan E. Hankinson, JoAnn E. Manson, Bernard A. Rosner, and Elizabeth R. Bertone-Johnson

* Correspondence to Dr. Christine Langton, Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts Amherst, 715 North Pleasant Street, Amherst, MA 01003-9304 (e-mail: clangton@umass.edu).

Initially submitted May 7, 2021; accepted for publication December 30, 2021.

Menopause

"permanent cessation of menstruation recognized after 12 consecutive months of amenorrhea with no other obvious pathological or physiological cause"

- Determinants of age at menopause
  - Number of oocytes at birth
  - Degeneration of oocytes due to atresia
  - Threshold oocytes needed to produce sufficient hormones to maintain menstrual cyclicity
- Average age 51

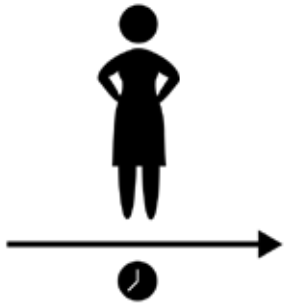


Image source adapted from Noun Project: Marie Van den Broeck

Early Natural Menopause

- Cessation of ovarian function before age 45
- Affects ~10% of women in Western populations
- Increased risk:
  - cardiovascular disease
  - osteoporosis
  - cognitive decline
  - premature mortality
- Interferes with family planning

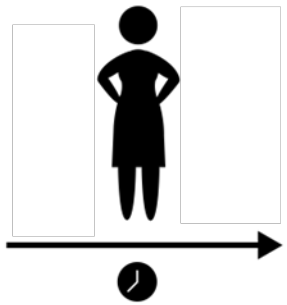


Image adapted from Noun Project: Marie Van den Broeck

Diethylstilbestrol (DES)

Increased Risk in DES daughters

- Clear cell adenocarcinoma of vagina and cervix
- Breast cancer
- Adverse reproductive outcomes
  - infertility
  - spontaneous abortion
  - ectopic pregnancy
  - preeclampsia
  - preterm delivery
  - stillbirth
  - neonatal death

Source: https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet#what-is-des

Ovarian Aging

Peak Reserve
4th month of fetal development

Birth | Menarche | Menstrual cycles | Menopause

~6-7m oocytes | ~1-2m oocytes | Recruitment & Atresia | ~1,000 oocytes

Oocyte Quantity

DES and Ovarian Aging

Peak Reserve
4th month of fetal development

~6-7m oocytes

- DES passes across placenta
- Animal studies
  - Absence of corpus luteum
  - Polyovular follicles
  - Ovarian cysts
- DES *may* affect:
  - Initial cohort of follicles
  - Rate of fetal oocyte atresia

Source: Reed CE, Fenton SE. Exposure to Diethylstilbestrol during Sensitive Life Stages: A legacy of heritable health effects. *Birth Defects Res C Embryo Today.* 2013;99(2):134-46.

Nurses' Health Study II

- Prospective cohort study
- 116,429 female registered nurses from 14 states
- Aged 25-42 years in 1989
- Questionnaires every 2 years, on-going
- Assess medical history and lifestyle behaviors
- Follow-up >89% for each cycle

Menopause Assessment

- Baseline and biennial questionnaires
  - Menstrual periods ceased permanently
  - Age at cessation
  - Natural cessation or due to surgery, radiation, chemotherapy
  - Use of hormone therapy
- Cases: natural menopause before age 45

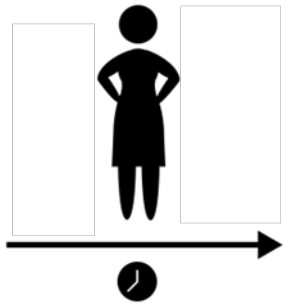
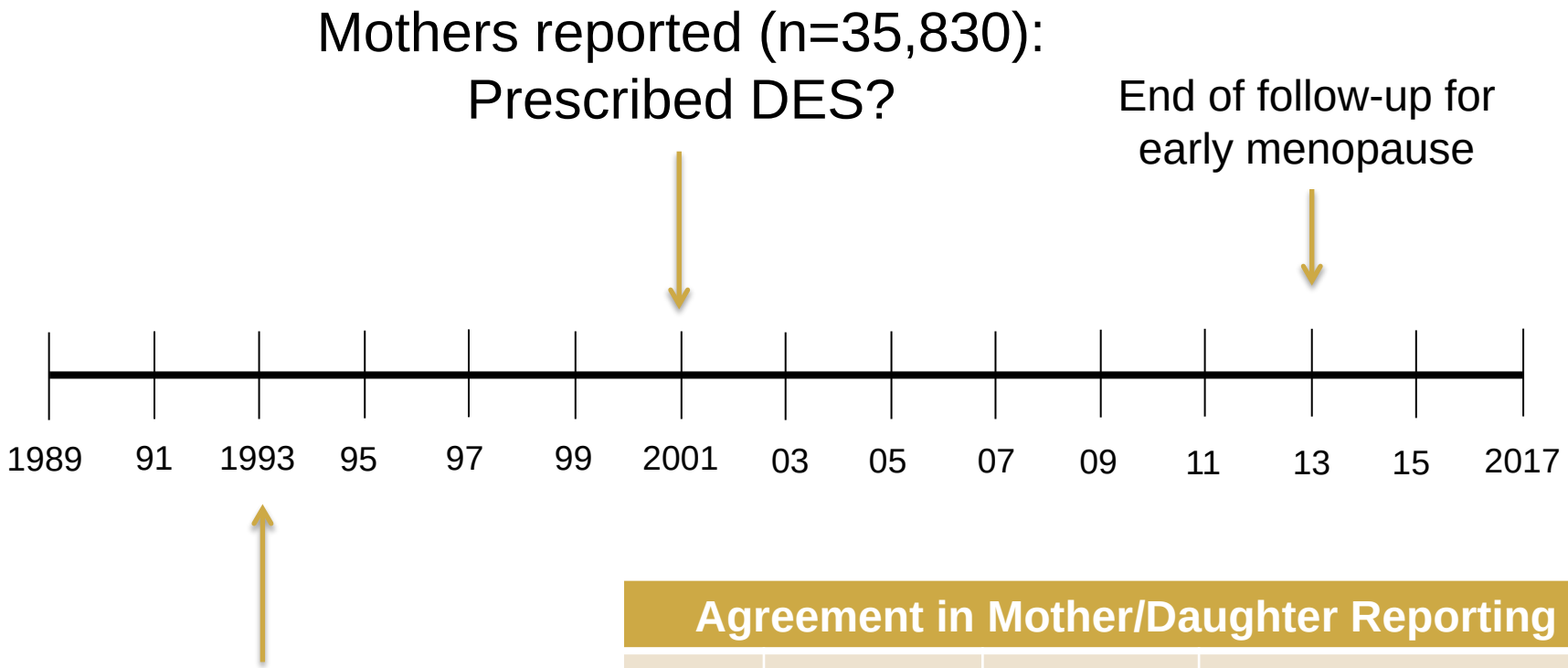


Image adapted from Noun Project: Marie Van den Broeck

DES Assessment, Participants and Mothers



Agreement in Mother/Daughter Reporting			
Yes	**No**	**Total**	**Kappa**
567	26,248	27,180	K=0.75 (95% CI: 0.72-0.77)

Statistical Models

- Cox proportional-hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs)

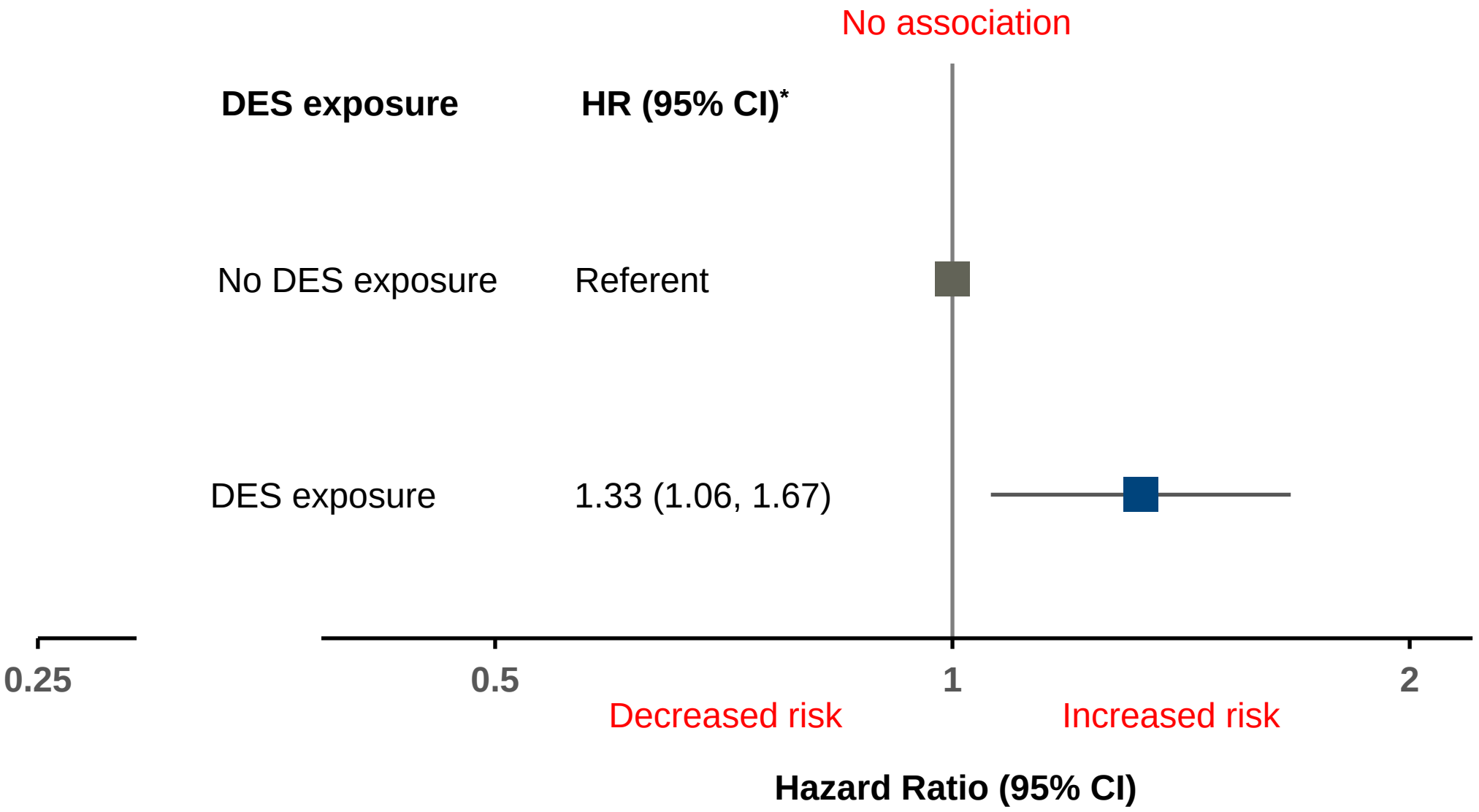
Model 1	Model 2	Model 3
Unadjusted	**Time-varying Participant Factors**	**In utero Factors**
§ Age as time scale	§ Age at menarche* § Smoking § Alcohol § BMI § Vitamin D § Menstrual cycle length § Infertility § Parity § Breastfeeding § Oral contraceptives § Tubal ligation	§ Part of multiple birth § Cigarette exposure § Prematurity § Birth weight

*Not time-varying

Demographics at Baseline

Characteristic	All Participants (n=106,633)	In utero DES exposure (n=2,401)
Age, mean	34.1	34.5
Non-Hispanic White	94%	97%
Cigarette smoking, pack-years, mean	17.9	13.0
Infertility due to ovulatory disorder	4.7%	7.8%

Risk of Early Menopause by In Utero DES Exposure



*Adjusted for age and questionnaire cycle (as time scale), age at menarche, time-varying smoking, alcohol, BMI, vitamin D, parity, breastfeeding, infertility, menstrual cycle length, oral contraceptives, tubal ligation, and other in utero exposures: cigarette smoke exposure, part of multiple birth, prematurity, birth weight.

Conclusions

In utero DES exposure and menopause

- **Increased risk** of early menopause (<45 years)
- Consistent with prior epidemiological studies
- Facilitate early identification for CVD risk reduction strategies
- Potential multigenerational effects

https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet#what-health-issues-might-des-grandchildren-have

Soy-based Infant Formula and Uterine Fibroids

ehp Environmental Health Perspectives

HOME ISSUE IN PROGRESS ARCHIVES COLLECTIONS AUTHORS REVIEWERS ABOUT INTRODUCING *JHP*

Open Access

Vol. 131, No. 1 | Research

Soy-Based Infant Formula Feeding and Uterine Fibroid Development in a Prospective Ultrasound Study of Black/African-American Women

Christine R. Langton, Quaker E. Harmon, Kristen Upson, and Donna D. Baird

Published: 25 January 2023 | CID: 017006 | https://doi.org/10.1289/EHP11089

Uterine Fibroids

- Non-cancerous tumors of myometrium
- >70% of reproductive age women
- Symptomatic fibroids can lead to severe morbidity and hysterectomy
- Black/African American women disproportionally burdened

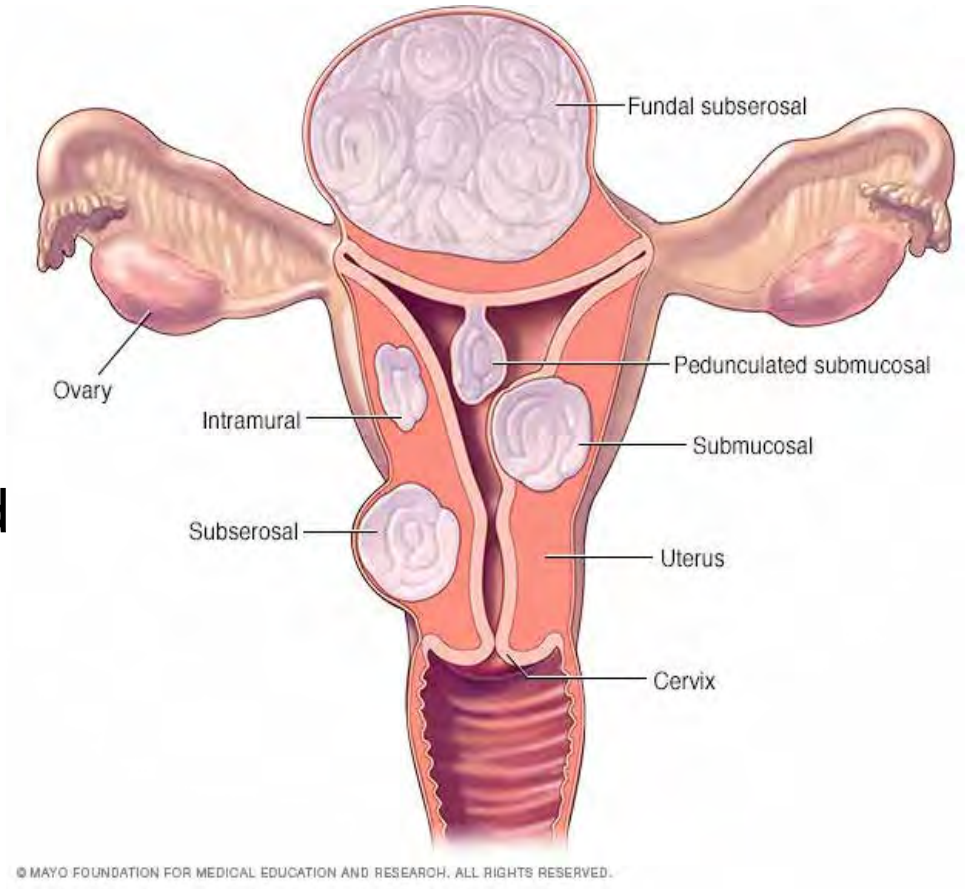
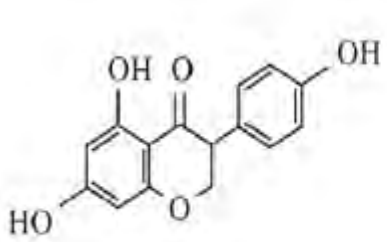
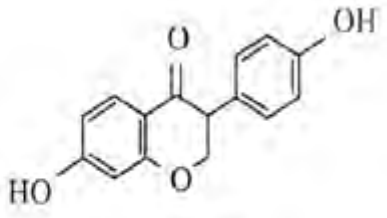


Image source: https://www.mayoclinic.org/diseases-conditions/uterine-fibroids/symptoms-causes/syc-20354288

Soy has Phytoestrogens

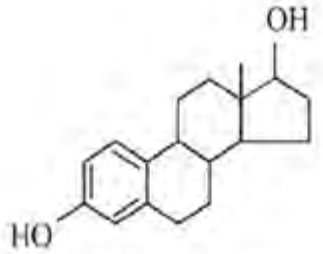


Genistein



Daidzein

≈



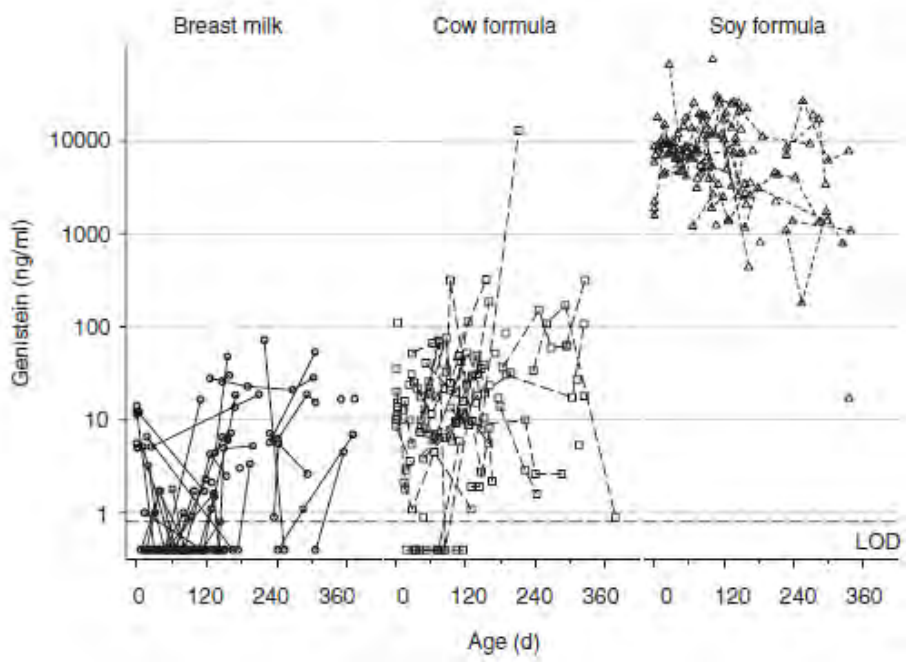
17-beta-estradiol

- Isoflavones act as endocrine disruptor
- Postnatal treatment to lab animals
  - Alters rodent reproductive tract including uterus (Suen et al. 2021)
  - Increased fibroid development in Eker rats (Greathouse et al. 2012)
- Exposure during sensitive developmental windows detrimental effects on reproductive systems

Image adapted: Pilšáková L, Riečansky I, Jagla F. The physiological actions of isoflavone phytoestrogens. *Physiol Res.* 2010;59(5):651-664.

Soy-based Infant Formula

- Linked to reproductive conditions
  - early/late menarche, menstrual irregularities, endometriosis
- Proliferative vaginal tissue and slower rate of uterine involution in soy-fed infants[1]
- Contains high levels of phytoestrogens
- Consumed by 12% US infants



[1]Adgent et al. A longitudinal study of estrogen-responsive tissues and hormone concentrations in infants fed soy formula. *J Clin Endocrinol Metab*. May 1 2018;103(5):1899-1909; Figure adapted: Cao et al. Isoflavones in urine, saliva, and blood of infants: data from a pilot study on the estrogenic activity of soy formula. *J Expo Sci Environ Epidemiol.*. 2009 Feb;19(2):223-224.

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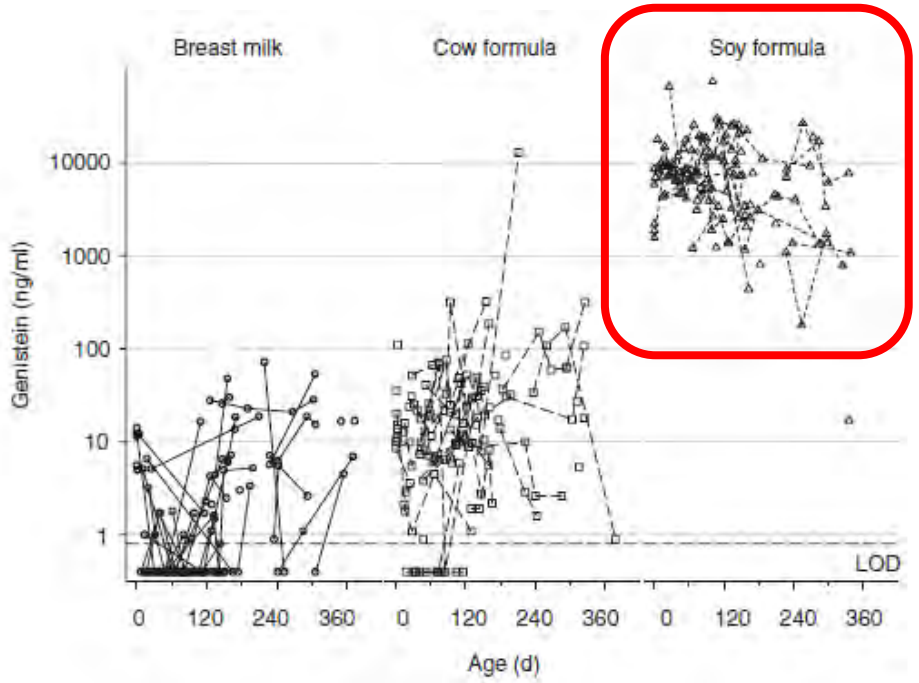

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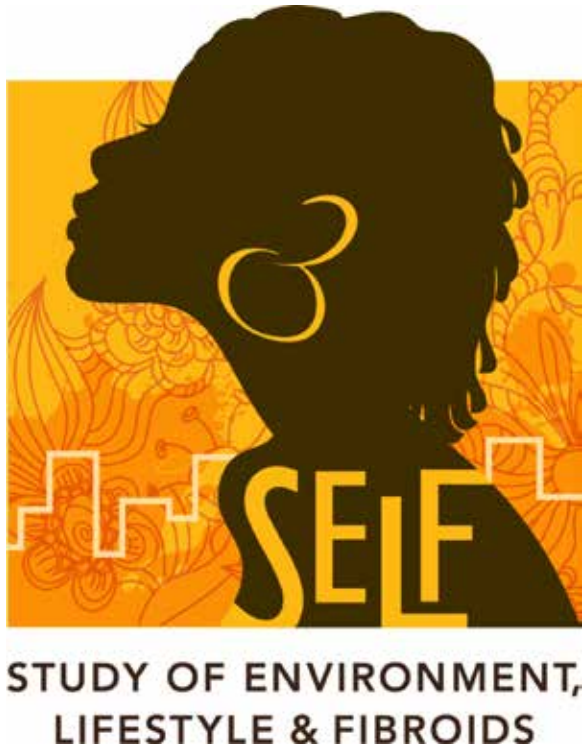
Study of Environment, Lifestyle & Fibroids (SELF)



- Prospective cohort with community-recruited participants (n=1,693)
- Detroit, Michigan area
- Self-identified Black or African American women
  - Ages 23-35
  - Premenopausal
  - No prior clinical diagnosis of fibroids

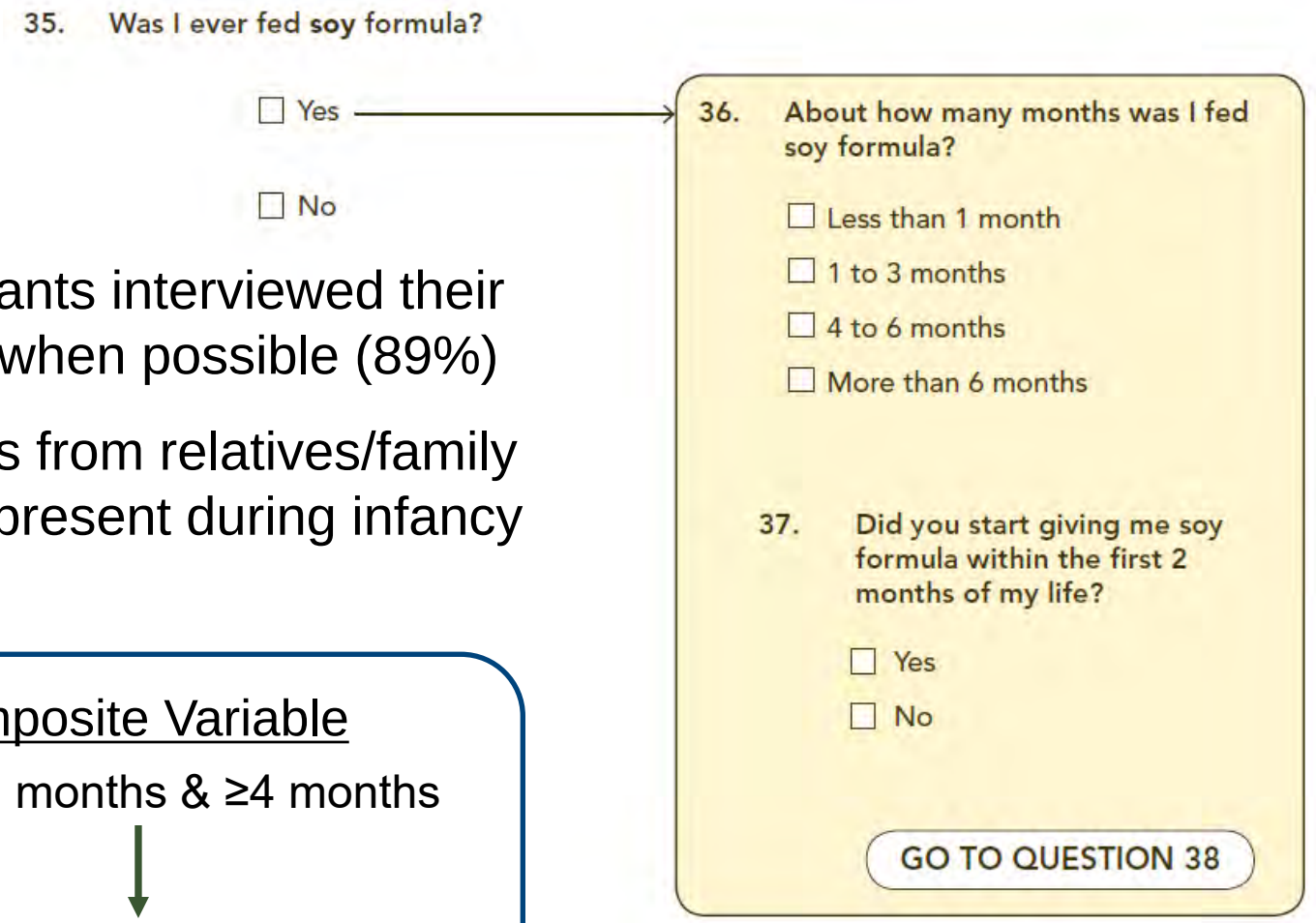
SELF – Study Design

Visit 1	Visit 2	Visit 3	Visit 4
n=1,693	88% response	86% response	91% response
2010–2012	2012–2015	2014–2016	2016–2018
	~18-20 mos.	~18-20 mos.	~18-20 mos.

Every visit

Ultrasound
Questionnaires
Clinical Measurements
Biospecimen

Soy Formula Assessment, Mothers Interviewed



35. Was I ever fed soy formula?

☐ Yes → 36. About how many months was I fed soy formula?

☐ Less than 1 month
☐ 1 to 3 months
☐ 4 to 6 months
☐ More than 6 months

☐ No

37. Did you start giving me soy formula within the first 2 months of my life?

☐ Yes
☐ No

GO TO QUESTION 38

- Participants interviewed their mother when possible (89%)
- Answers from relatives/family friends present during infancy (11%)

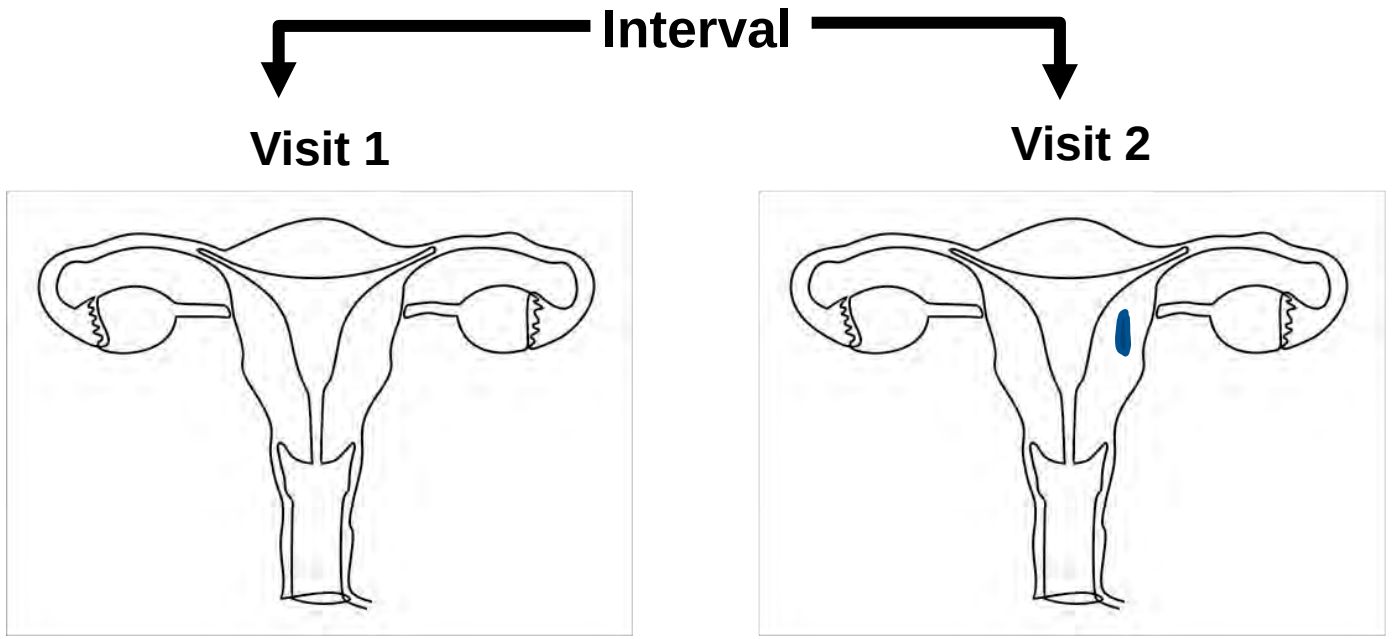
Composite Variable

Within 2 months & ≥4 months

↓

More exposed

Fibroid Incidence, n=1,121 participants



Eligible — No prior fibroid

Outcome — New fibroid case

Model — Cox regression, with age as time scale

Covariates

Model 1	Model 2	Model 3
Unadjusted	**Maternal and Early Life Factors**	**Time-varying Participant Factors**
§ Age as time scale	§ Mother's age at birth § Mother's education § Maternal pregnancy complications § Birth weight	§ BMI § Income § Smoking § Parity § Years since last birth § Years since last contraceptive injection

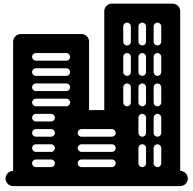
Demographics of SELF Cohort (n=1,610)

Mean age 29 Y (SD 3.4)

45% household income <$20,000

78% some college

60% had a birth



60% employed

13% fed soy formula

Image sources: Birthday cake, SBTS; Education, Imran Shaikh; Building, Ralf Schmitzer; Birth, David Khai.

Demographics by Soy Formula Feeding in Infancy*

Characteristic	Never Fed (n=971)	Ever Fed (n=150)
Participants' mothers:		
Age ≥30 years at participant's birth	19%	26%
≥4 years college	10%	17%
Participants at enrollment:		
Age 23-25 years	25%	33%
Current smoker	20%	13%
Household income <$20,000	46%	43%
Ever use of contraceptive injection	48%	42%

*Among 1,121 fibroid-free participants at enrollment.

Demographics by Soy Formula Feeding in Infancy*

Characteristic	Never Fed (n=971)	Ever Fed (n=150)
Participants' mothers:		
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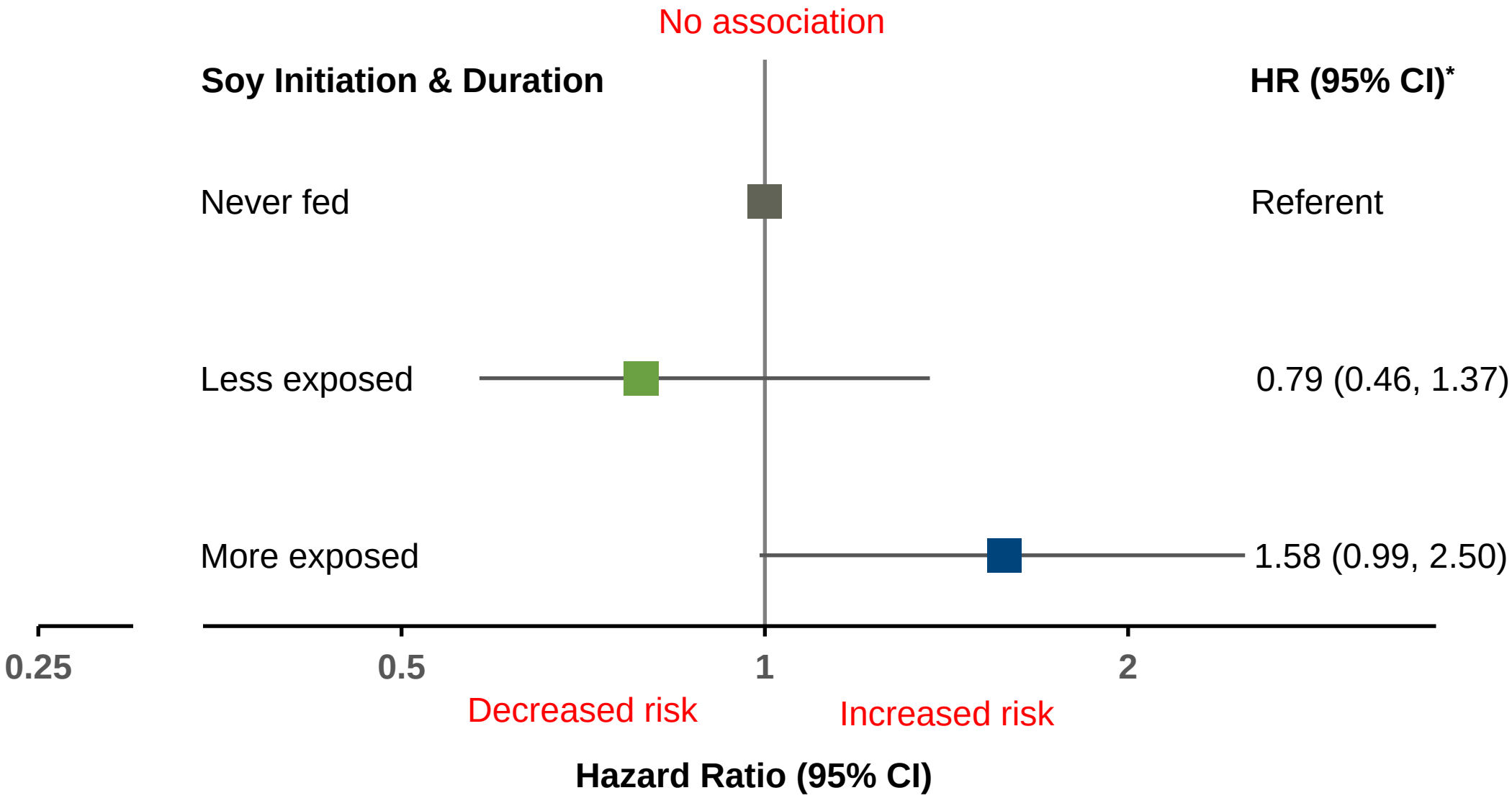
*Among 1,121 fibroid-free participants at enrollment.

Risk of Incident Fibroids by Soy Formula Feeding

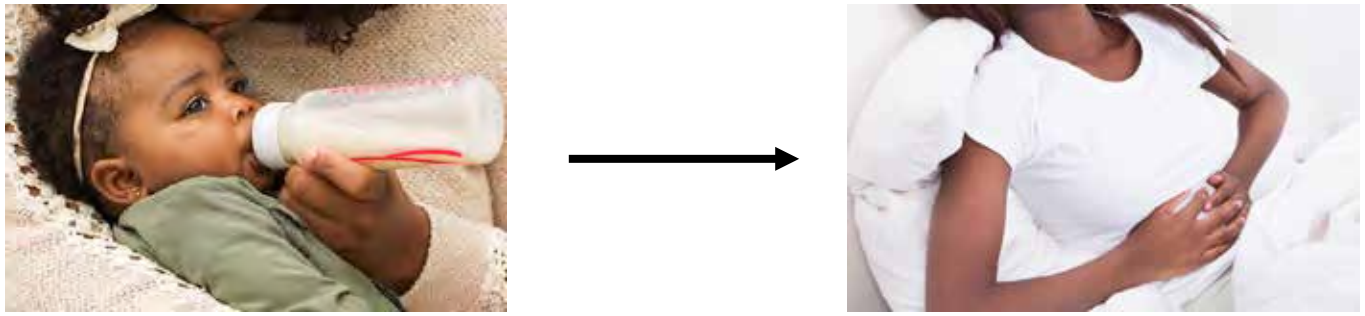


*Adjusted for age (time scale), maternal pregnancy complications, mother's age at participant's birth, mother's education, birth weight, and time-varying: BMI, income, smoking, parity, time since last birth, time since last contraceptive injection.

Conclusions

Soy-based infant formula and uterine fibroids

- **Increased risk** of ultrasound-identified incident fibroids in adulthood for those fed **soon after birth and for a longer duration**
- Consistent with prior animal and human studies
- Biological pathway is not established



Summary

- Prenatal/early life exposures affect reproductive tract and organs influencing health and disease later in life
- More research needed to understand mechanisms

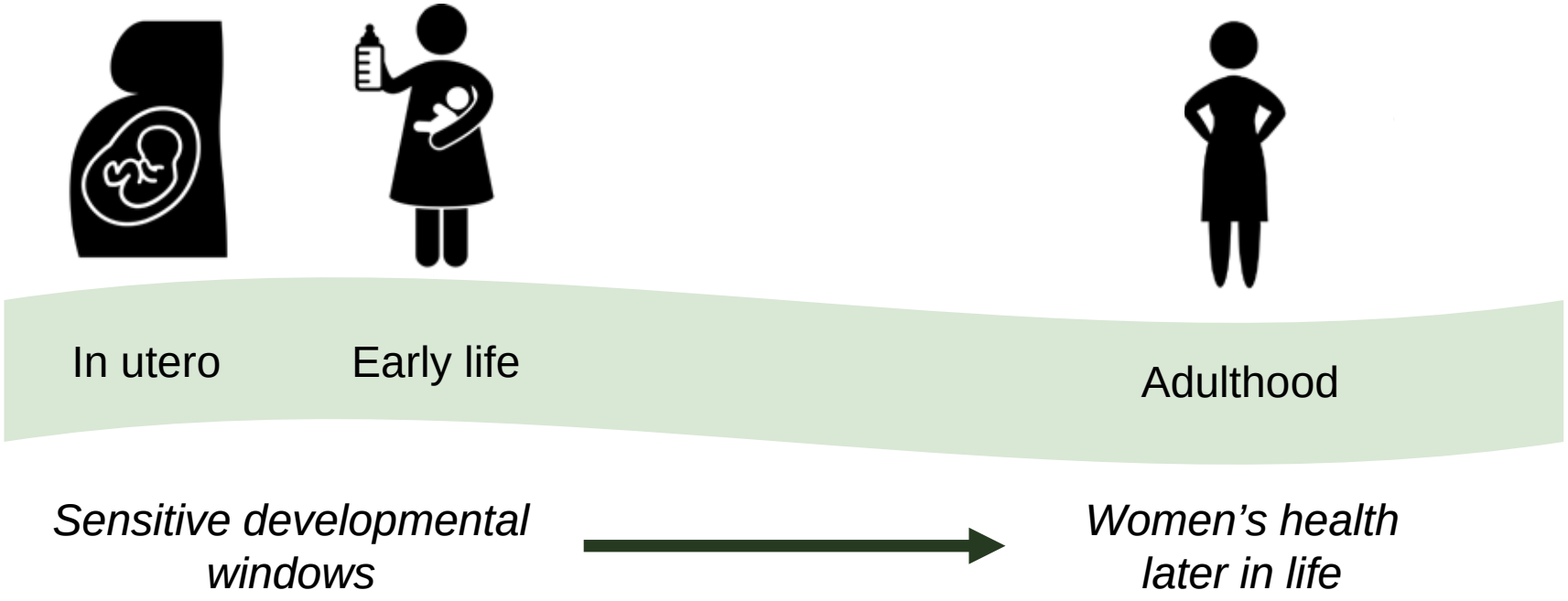


Image sources from Noun Project: Fetus, Lars Meiertoberens; Midwife, Gan Khoon Lay; Female aging, Marie Van den Broeck.

Collaborators and Funding

DES and Menopause:

Elizabeth Bertone-Johnson (PI/mentor)
Susan Hankinson
JoAnn Manson
Alexandra Purdue-Smithe
Bernard Rosner
Lynnette Sievert
Brian Whitcomb

Funding: Supported by UO1CA176726 and RO1HD078517 from the NIH/DHHS.

Soy Formula and Fibroids:

Donna Baird (PI/mentor)
Quaker Harmon
Kristen Upson

Funding: Supported by the Intramural Research Program of the NIH, and funds from the American Recovery and Reinvestment Act.

Questions: christine.langton@nih.gov

Closing Remarks

Michelle Bolek
Director, Division of Strategic Communications
Office on Women's Health
U.S. Department of Health and Human Services

Thank you

Visit the Symposium Website for More!

Join us tomorrow at 9am eastern for day 2 of the symposium.

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Endocrine Disrupting Chemicals and Women's Health Symposium

A Virtual Symposium

July 18–19, 2023

9am–4pm ET

OASH | Office on Women's Health

Welcome

Admiral Rachel L. Levine, MD
Admiral, U.S. Public Health Service
Assistant Secretary for Health
U.S. Department of Health and Human Services

Successful Interventions To Ameliorate the Impact of EDCs

Linda Giudice, M.D., Ph.D.

Moderated by LT Abayomi Walker

Successful Interventions to Ameliorate the Impact of EDCs

Linda Giudice, M.D., Ph.D.

Distinguished Professor of Obstetrics, Gynecology and Reproductive Sciences

University of California, San Francisco

Successful Interventions to Ameliorate the Impact of EDCs

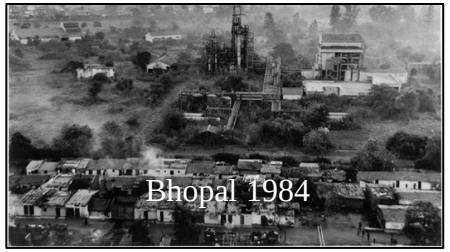
Linda C. Giudice, MD, PhD
Distinguished Professor
Founder UCSF Program on Reproductive Health and the Environment
University of California San Francisco
Past Chair, FIGO Committee on Climate Change and Toxic Environmental Exposures

No disclosures

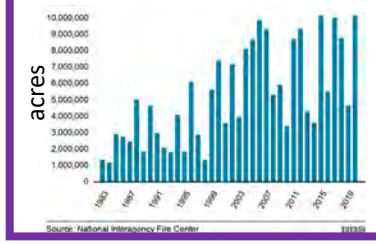
Endocrine Disrupting Chemicals and Women's Health Symposium
Office of Women's Health
U.S. Department of Health and Human Services
July 18-19, 2023

Why Am I Giving This Presentation?

- As a physician in reproductive medicine
- As a concerned citizen of the world



U.S. Land burned by fires
1983-2020

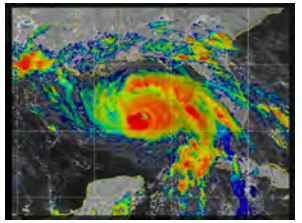


Brazil severe fires
2020

Severe fires Europe, China
U.S., other 2021

Massive flooding UK, Europe,
China, Amazon 2021

Hurricanes
IR map Ida Aug 28 2021



Objectives

- Identify EDC exposures and who is at risk for impaired health outcomes
- Understand models of evidence of harm and challenges to getting evidence about interventions to ameliorate EDC impacts
- Learn about evidence showing interventions successfully ameliorate the impact of EDCs

Exposures to EDCs

The backbone of intervention strategies

Environmental and Occupational

General Population:

- Diet (food, drink)
- Personal care products (BPA)
- Cosmetics (phthalates)
- Plastics (phthalates, BPA)
- Textiles
- Construction materials
- e-waste (Br, Cl flame retardants)
- Digital receipts
- Pesticides – home use, food
- Air pollution – O_3, PM, Pb, diesel
- Household
  - dust/furniture (PBDEs, CH_2O)
  - Cleaning products

Occupational Exposures:

- Pesticides (agricultural workers)
- Phthalates, benzophenones, parabens, siloxanes (cosmetologists, hair dressers, nailists)
- Organic solvents/alkyl phenols (agricultural workers, life science technicians)
- Phthalates, drugs (health care workers)
- Many others…..

– Common: Every person in U.S. has contaminants, mixtures are the rule, babies are born “pre-polluted”

Some differences: doses, duration of exposures, methodologies to evaluate exposures, measurements, race/ethnicity, SES

Woodruff TJ, et al, Environ Health Perspect 2011;119:878–885; US DHHS. President’s Cancer Panel 2008–2009 Annual Report. Available at: https://deainfo.nci.nih.gov/advisory/pcp/annualreports/pcp08-09rpt/pcp_report_08-09_508.pdf; Birnbaum LS Trends Endocrinol Metab 2013;.24:321-323

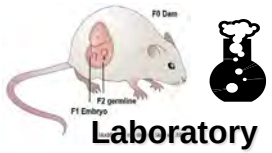
Who is at risk?

- ***Everybody* but some more than others**
  - **Most vulnerable**:
    - children
    - pregnant persons
    - the elderly
    - those with chronic diseases
    - marginalized populations
    - low sociodemographic status
    - workers in hazardous jobs

How do we know when and how EDCs increase risk of adverse health outcomes?

The Scientific Evidence

- **Animal and *in vitro* human cell models** – mechanisms
- **Epidemiologic studies** reveal data ***correlating*** environmental exposures and human health outcomes.
- **Navigation Guide** (bridging clinical and environmental health)
- **Mixture risk assessment** (MRA statistical modeling)
- **Job exposure matrices (JEM)** (occupational health intersection)
- **Systematic reviews, scoping reviews, meta-analyses**
- **Wildlife** observations



Laboratory


Humans

Modeling/informatics


Wildlife

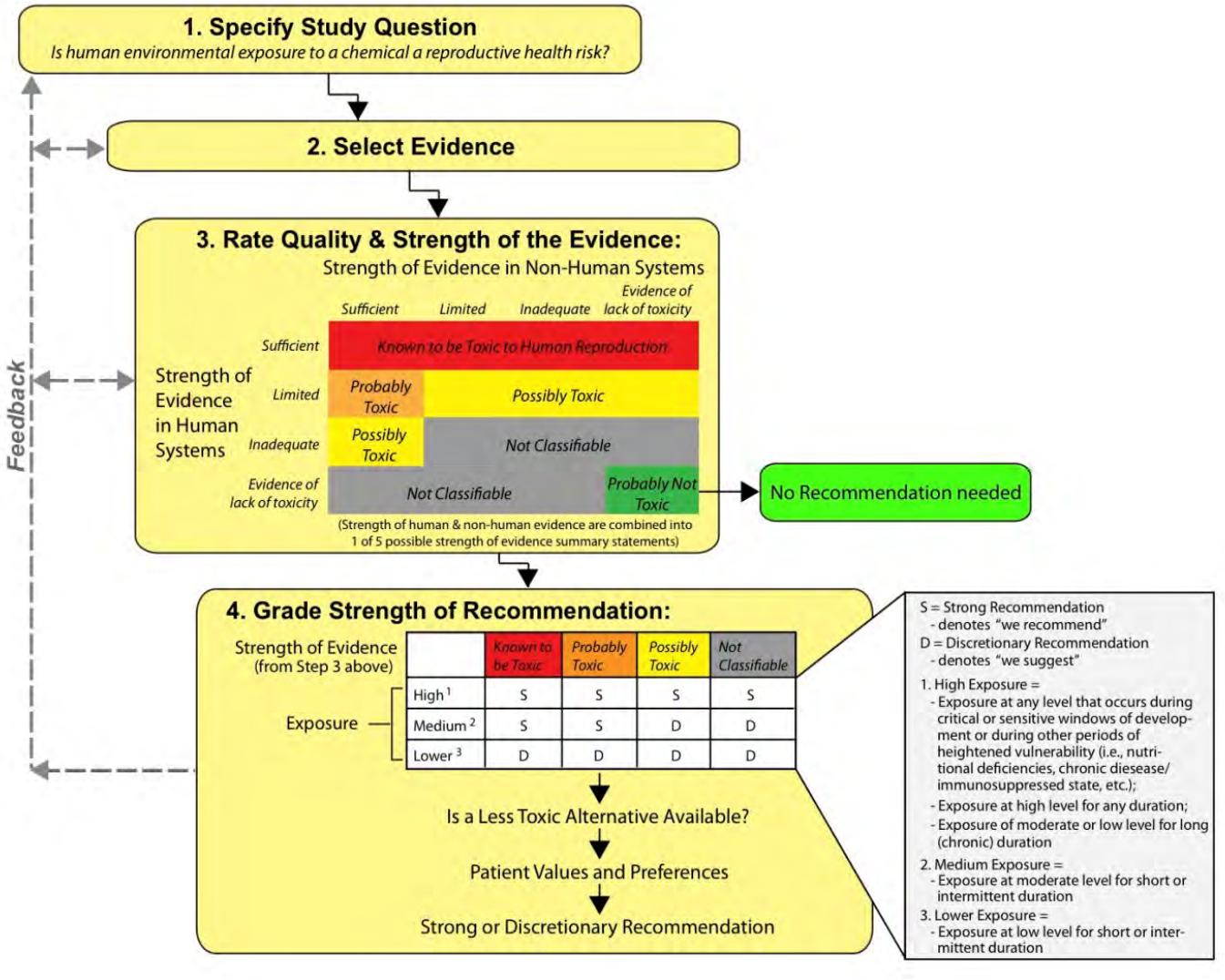
How to Bridge Clinical and Environmental Health?

THE COCHRANE COLLABORATION®

Organizes research findings and facilitates evidence-based interventions involving health professionals, patients and policy makers.

GRADE

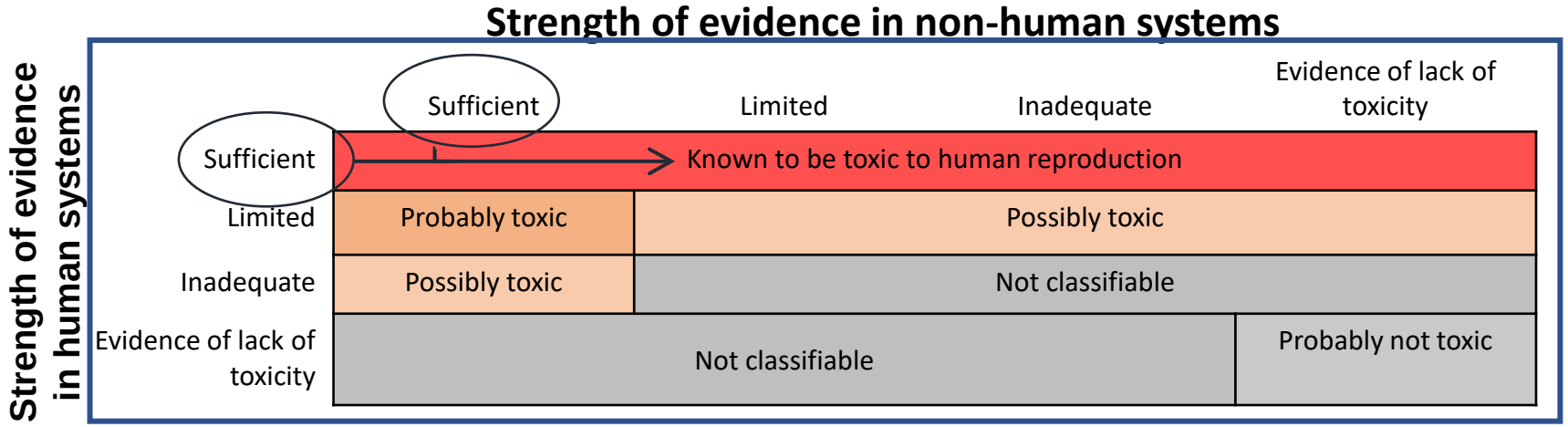
Systematic approach to rate certainty of evidence in systematic reviews and other evidence syntheses



The Navigation Guide: A rulebook for "moving from knowing to doing"
Woodruff and Sutton Environ Health Perspect 2009, 2014

Evidence integration - an example of PFOAs and IUGR

Woodruff TJ, et al. Health Aff (Millwood) 2011;30:931–937.



***Conclusion*: Human exposure to *PFOA is known to be toxic* to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and non-human mammalian species.**

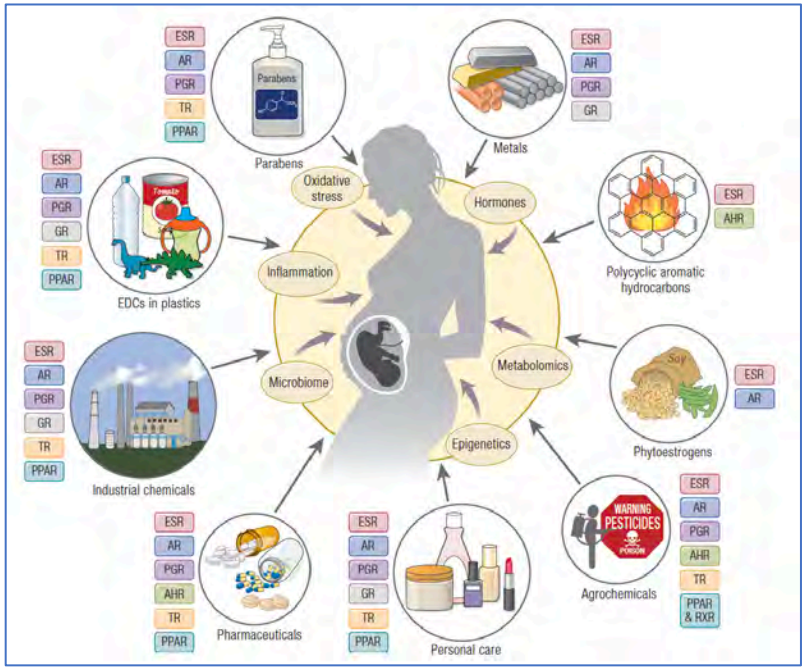
The Navigation Guide, Cochrane and GRADE have been acclaimed as exemplary approaches for transparency, rigor, and reproducibility by the National Academy of Medicine.

NRC. Review of EPAs Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press, 2014

Labor and time intensive and expensive, one by one approach

Challenges to Intervention Strategies
A Case Study: Pregnancy

Humans are exposed to multiple chemicals of different classes with similar or differing signaling mechanisms that can lead to synergistic, additive, antagonistic or no effect on physiologic outcomes



Padmanabhan et al. Endocr Reviews 2021;42:295-353

Challenges in Risk Assessment, Data Interpretation, and Quality Evidence for Intervention Strategies: *Pregnancy*

- What to sample? (maternal urine, plasma/serum, placenta, cord blood, amniotic fluid)
- Most studies sample at a single gestational time point
- Inconsistent attention to:
  - Fetal organ-specific differences in susceptibility windows across gestation
  - fetal sex can modulate EDC effects
  - confounders (ethnicity, age, diet, pre-pregnancy weight, weight gain, lifestyle factors)
  - mixtures
- Some cohorts now following the children longitudinally
- Less focus on correlations and subsequent maternal morbidities (e.g., T2D, CVD)

Padmanabhan et al. Endo Reviews 2021;42:295-353

Mixture Risk Assessment (MRA)

Maternal exposures to ***same chemical class*** (e.g., phthalates) or **same mechanism of action** (e.g., xenoestrogens). *Padmanabhan et al. Endo Reviews 2021;42:295-353*

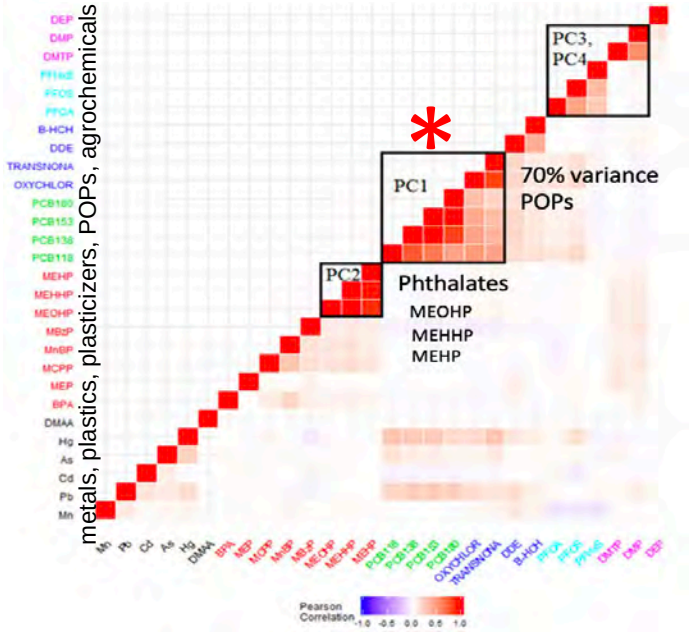
- 1st Δ maternal serum POPs = weak association with LBW; as a class (OC pesticides, PBDE, PCB mix)→ **strong associations**.

Exposures to **Mixtures of Different EDC Classes** Assessed by **Statistical Modeling**

Lee et al. Identification of chemical mixtures to which Canadian pregnant women are exposed: The MIREC Study. Environ Intl 2017;99:321-330.

- 50 chemicals, **divergent characteristics and dis/similar modes of action** in maternal & fetal samples
- **statistical modeling, clustering and PCA** to understand impact of complex chemical mixtures, between/among chemicals, geographic locations, SDS
    - **PC1 associated with lower SDS, BMI>25***

Heat Map of Pearson Correlation Matrix of 28 Chemicals



Challenges:

- Current regulatory guidelines of allowable concentrations of environmental EDCs were developed on chemical-by-chemical basis.
- Statistical modeling needs standardization as several inputs with increased rigor including biomonitoring approaches .

Job Exposure Matrix Hx, Methodology, Exposure Scores

2002: Occupational exposure to EDCs and risk of hypospadias and cryptorchidism in UK.
2009 Brouwers updated → basis for emerging JEMs

- **353 Job classifications identified** (UK Standard Occupational Classification 2000 (SOC2000))
- **Exposure risk scores**: 0-9 (no, low, medium, high exposure levels)
- **Scoring chemical categories, subcategories and occupational setting** –from environmental health literature, agencies, WHO *Global Assessment and State of the Science on EDCs*.
- **Result: 10 Chemical groups** (& 33 subgroups)

Job Exposure Matrix 5 Different Job Titles

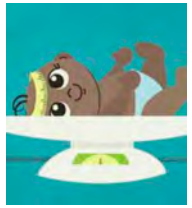
SOC2000 job title	Exposure Score	Chemical Group
Senior govt officials	0	-
Electrical workers	1	Metals
Glass ceramic makers Decorators	2	Organic solvents Metals
Beauticians/related occupations	2	Phthalates Organic solvents Alkylphenolics
Chemical processors	9	Multiple

Challenges: Differences in exposures over time; +/- task-specific information (questionnaires, interviews) to minimize job misclassification; Biomonitoring data; methodologies for evaluating

Van Tongeren et al. Annals Occup Hygeine 2002;;46:465-477;Brouwers et al. Occup Environ Med 2009;66_607-614.

Occupational Exposure to EDCs and Birth Weight and Length of Gestation

A European Meta-analysis



Study:

- N=133,957 mother-child pairs in 13 European cohorts; births 1994 - 2011
- Maternal job titles were linked with exposure to 10 EDC groups assigned in a JEM.
- Birth outcomes were correlated with exposure categories (0,1,2,3,9); meta-analysis of cohort-specific estimates.

Results:

- 11% of pregnant persons were exposed to EDCs at work in pregnancy based on job title
- **Exposure to ≥1 EDCs** was associated with **increased risk of term LBW** (OR 1.25; 95% CI 1.04-1.49)
- **Risk increased** with exposures to **increasing # of EDC gr**oups: OR 2.11; 95% CI: 1.10-4.06 (>4 EDCs)
- **Highest risk jobs**: **agricultural workers, house cleaners, hairdressers, medical assistants**
- **Data were consistent across all cohorts**

Conclusion: employment during pregnancy in occupations classified as possibly or probably exposed to EDCs was associated with an increased risk of term LBW.

Birks et al. Environm Health Persp 2016; 124:1785-1793

Intervention Studies to Ameliorate EDC Effects

- Animal
  - epigenetic modifiers to rescue phenotypes
- Human:
  - Individual level
  - Policy changes
  - Entrepreneurial opportunities (“safer alternatives”)
- Education
- Advocacy

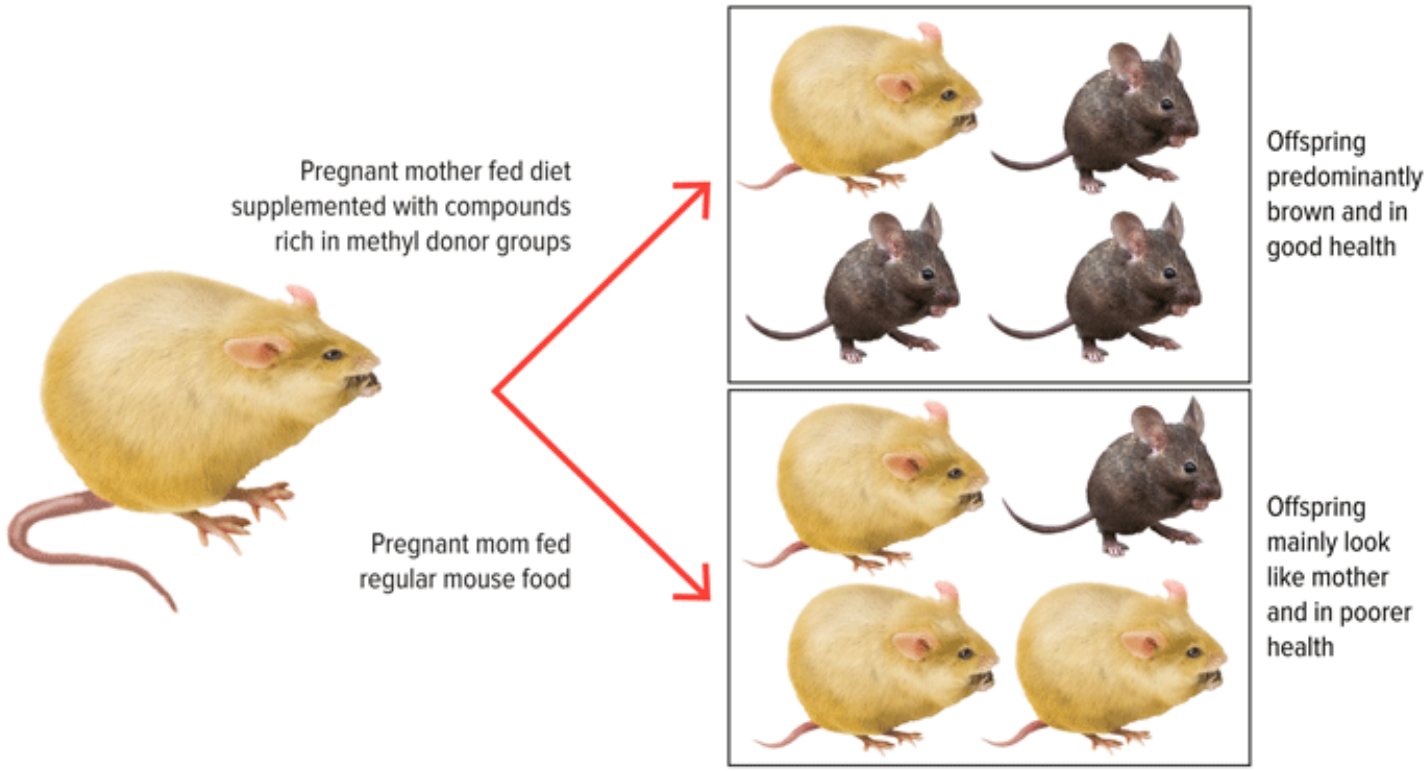
What is the evidence that interventions will impact EDC levels?

What is the evidence that interventions will improve health?

Agouti Mouse Model Shows Maternal Diet and BPA Influence Fetal Development that Intervention Reverses

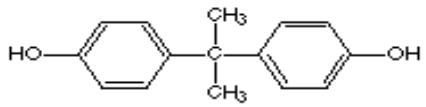
Genetically identical mice but different color (brown, yellow) and size Agouti gene product binds to melanocortin R blocking black pigment and is involved in feeding behavior and weight set point

Normal healthy mice – agouti gene is methylated and is off.
Yellow, obese sisters – agouti gene is unmethylated and is on.

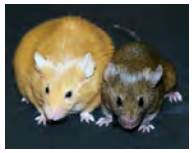


(Dolinoey 2007, Zeisel 2009)

Estrogen-like EDCs in Pregnant Dams Trigger the Agouti Phenotype in Pups and Me Donors Rescue the Phenotype



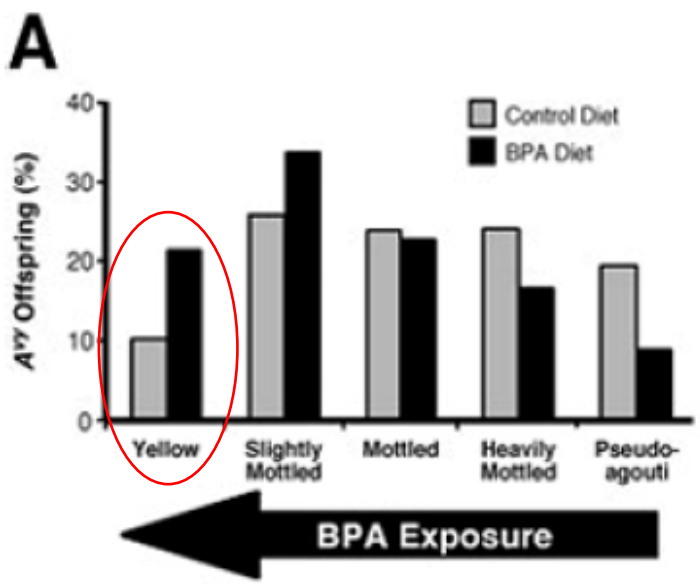
Bisphenol A

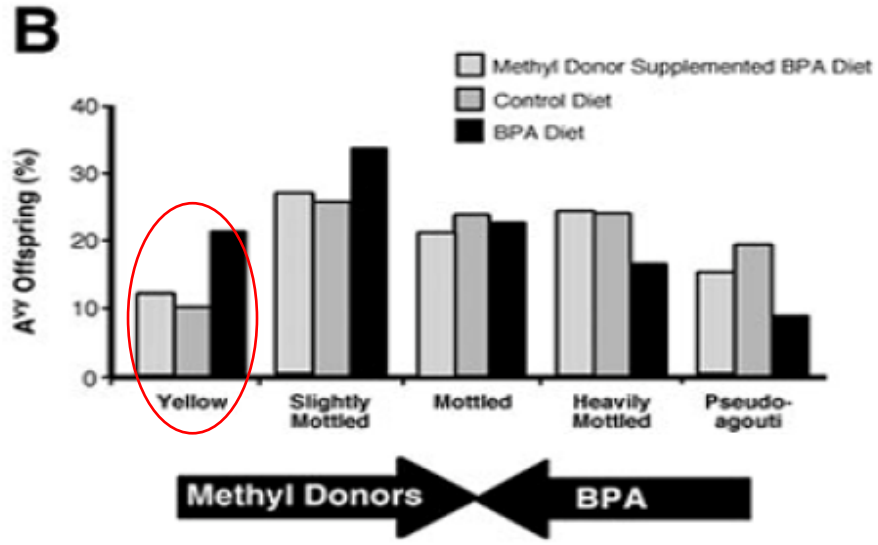


Environmental “protection”
Folic acid and Vitamin B12
rescue the phenotype

- higher ratio of yellow, obese progeny than expected
- global DNA hypomethylation
- 30% agouti gene DNA me sites

- increased DNA methylation
- normal ratio of pups



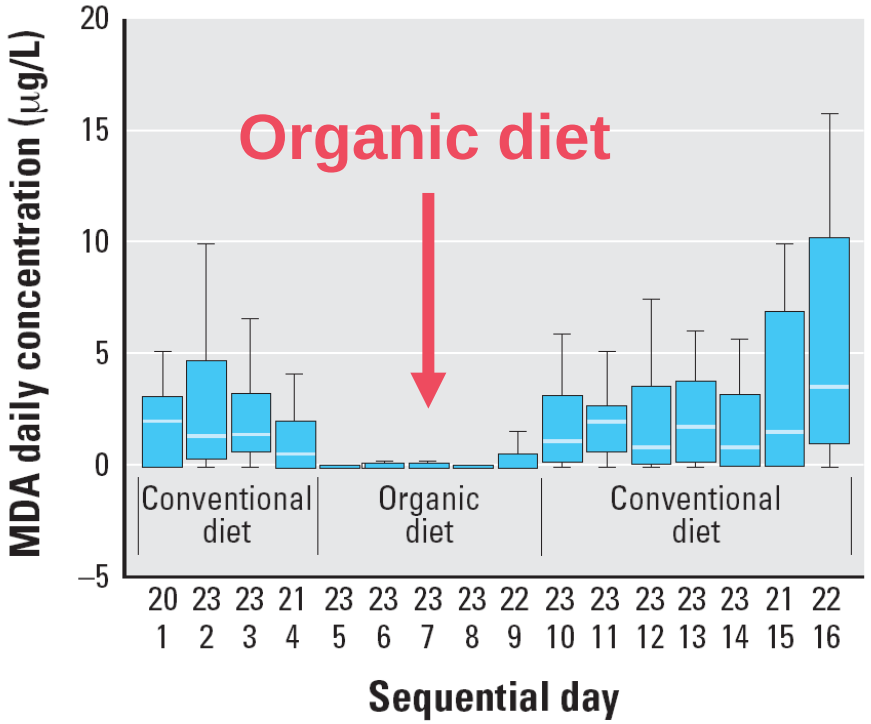


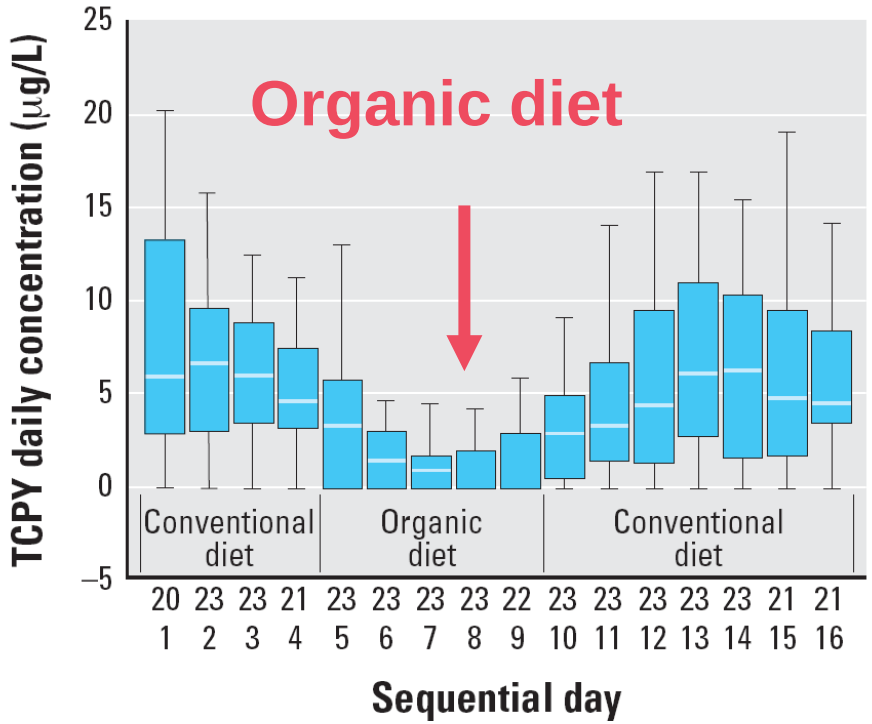
(Dolinoey 2008)

Interventional Studies Humans

- Diet
- Personal Care Products
- Household Products

Dietary Interventions in Children Can Reduce EDC Exposure





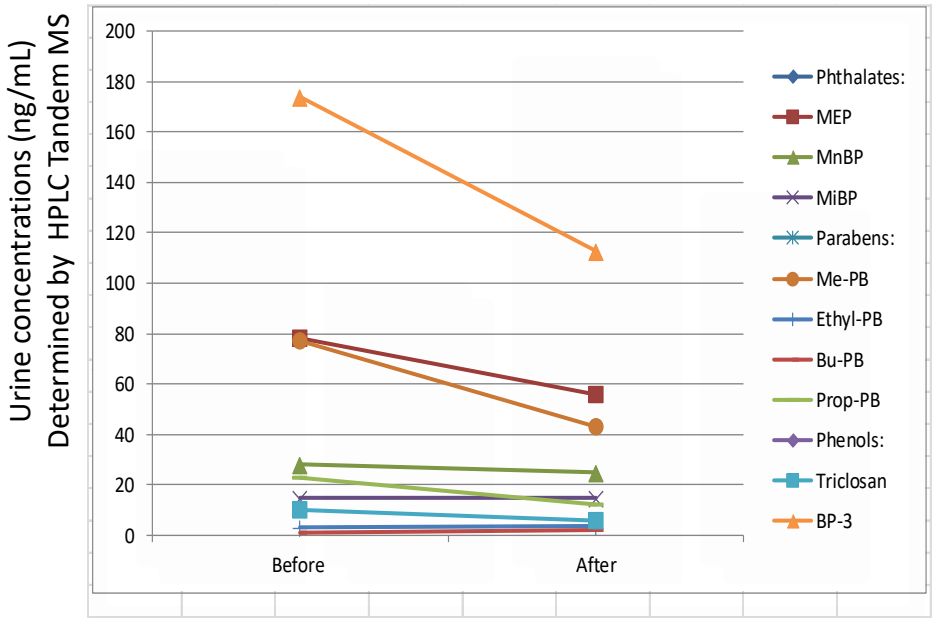
- 23 children monitored for metabolites before/after organic diet
- Levels of urinary metabolites for chlorpyrifos and malathion reduced to non-detectable
- Again elevated on re-introduction of conventional diet

Source: Lu C et al. 2006. Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. Environ Health Perspect. 2006 Feb;114(2):260-3.

The HERMOSA Intervention Study

Personal Care Products

100 Latina girls in Salinas Valley community-based participatory research study to determine if using personal care products for 3 days would change urinary levels. Given OTC products without triclosan, BP-3/oxybenzone, parabens, phthalates



Analyte	Preintervention DF (%)	Preintervention GM (SE)	Postintervention DF (%)	Postintervention GM (SE)	Percent change (95% CI)[a]	Girls with decrease (%)
Phthalates						
MEP	100	78.2 (1.1)	99	56.4 (1.1)	−27.4 (−39.3, −13.2)	68
MnBP	97	28.3 (1.1)	98	25.1 (1.1)	−11.3 (−22.2, 1.1)	58
MiBP	99	15.2 (1.1)	99	15.2 (2.3)	−0.5 (−12.6, 13.3)	55
Parabens						
Methylparaben	93	77.4 (1.2)	87	43.2 (1.2)	−43.9 (−61.3, −18.8)	61
Ethylparaben	55	2.9 (1.2)	63	4.2 (1.2)	47.3 (−0.7, 118.4)	45
Butylparaben	49	0.8 (1.2)	62	1.7 (1.2)	101.7 (35.5, 203.2)	39
Propylparaben	90	22.6 (1.3)	87	12.3 (1.2)	−45.4 (−63.7, −17.9)	63
Phenols						
Triclosan	93	9.5 (1.3)	90	6.1 (1.2)	−35.7 (−53.3, −11.6)	65
BP-3	97	173.8 (1.2)	97	113.4 (1.2)	−36.0 (−51.0, −16.4)	65

Abbreviations: DF, detection frequency; GM, geometric mean; SE, standard error.
[a]From mixed-effects model adjusting for time of urine collection (using 24-hr clock hours and minutes).

This study demonstrates that techniques available to consumers, such as choosing personal care products that are labeled to be free of phthalates, parabens, triclosan, and BP-3, can reduce personal exposure to possible endocrine-disrupting chemicals.

Harley KG, Kogut K, Madrigal DS, Cardenas M, Vera IA, Meza-Alfaro G, She J, Gavin Q, Zahedi R, Bradman A, Eskenazi B, Parra KL. 2016. Reducing phthalate, paraben, and phenol exposure from personal care products in adolescent girls: findings from the HERMOSA Intervention Study. Environ Health Perspect 124:1600.

Nutritional Interventions to Ameliorate the Effects of EDCs on Human Reproductive Health - A Semi-structured Review by FIGO

Objective

To analyze evidence on nutritional interventions to reduce the negative effects of EDCs on reproductive, perinatal, and obstetric outcomes.

Search strategy

Searched MEDLINE (PubMed), Allied Health Literature (CINAHL), EMBASE, Web of Science, and Cochrane Database to 2009 - 2021.

Selection criteria

Experimental studies on human populations.

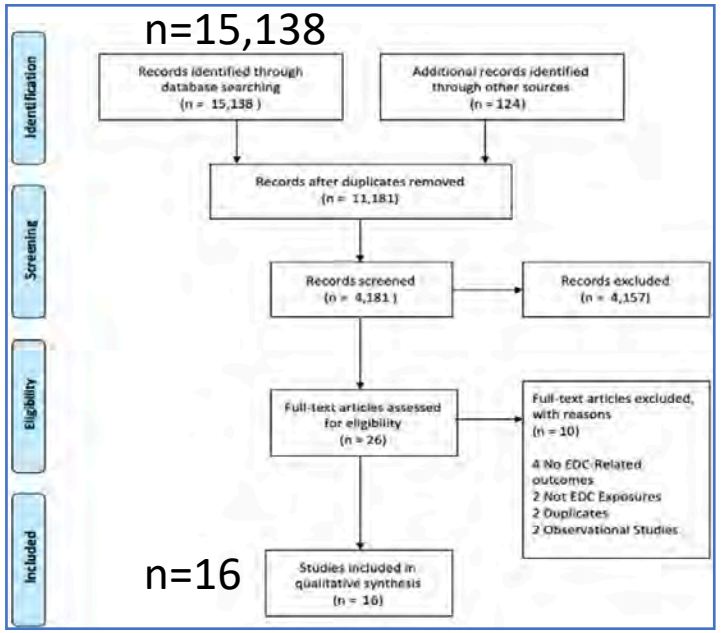
Data collection and analysis

Data were collected from eligible studies.

Risk of bias assessment was completed using the Cochrane risk of bias tool and the ROBINS-I Tool.

Corbett GA, Lee S, Woodruff TJ, Hanson M, Hod M, Charlesworth AM, Giudice LC, Conry J, McAuliffe FM and the FIGO Committees on Impact of Pregnancy on Long-term Health and Climate Change and Toxic Environmental Exposures *Int J Gynecol Obstet.* 2022;157:489.

Characteristics of the 16 studies



Population:

- Study size range 15–355 participants
- 3 included pregnant participants
- 6 included young healthy participants
- 2 included families (parents and children)
- 2 examined interventions in solely school-going children
- 4 included mixed-gender populations:
  - T2DM patients, cardiac atheromatous disease,
  - men and women aged over 60 years.

Risk of Bias:

- 7 were RCTs
- 3 RCTs crossover trials
- *6 non-randomized experimental trials*

Corbett IJGO 2022

Results of Some Intervention Randomized Trials

Study	Design, Population, n	Intervention Active Group	Findings
Carwile, 2011	Randomized single-blinded X-over trial Univ students/ staff n=75	Effect of canned (control) vs fresh soup x 5 days, 2 days washout between X over on urinary [BPA].	Int: 1.1 μg/L 95% CI 0.9-1.4 C: 20.9 μg/L, CI 17.9-24.1
Bae, 2014	Randomized double blinded X-over trial N-120 people >60 yo	Effect of canned (control) vs glass containers for drinking beverages on urinary BPA levels and blood pressure. 1 week each intervention, 1 week washout	Mean urinary BPA levels: Int: 1.13 μg/L ± 1.76 (SD) C: 7.93 μg/L + 6.02 No BP changes.
Hagobian, 2017	Double blinded RCT. N=24 researchers, lab staff, college women, nml BMI	Impact lifestyle interventions (education, BPA-free tupperware, H_20 bottles, cosmetics, hygiene feminine products; organic foods packaged in BPA-free glass/cardboard containers vs control with weekly newsletter/education on uBPA levels. 3 weeks duration	Significant (p=0.04) Rx × time Int effect on [BPA]. By 3 wks Int decreased mean u[BPA] by 0.71 ng/mL vs controls with increased u[BPA] by 0.32ng/mL (p = 0.04).

CONCLUSIONS:

- Evidence supports organic food consumption and avoiding plastics and canned foods and beverages reduce dietary exposures to EDCs.
- No fast foods, iodine supplementation, vegetarian diet, fatty fish diet, altering personal care products, removing dust are all supported by evidence to lower EDCs (some multiple EDCs).

- **CAVEATS**:
  - disparities in access to and affordability of organic foods, glass and stainless-steel bottles/containers
  - Most studies are still one EDC at a time. If BPA is decreased and phthalates not, what might be the consequences from a health perspective where people are exposed to mixtures not 1 EDC at a time?
  - So far rare evidence that reductions of EDCs lead directly to health improvement.

Risk Management and Healthcare Policy
2022;15:779-791
Open Access Full Text Article
Dovepress
REVIEW

Interventions on Reducing Exposure to Endocrine Disrupting Chemicals in Human Health Care Context: A Scoping Review

Jeongok Park [1,2], Hyejung Lee [1,2], Sejeong Lee [3], Hyojin Lee [3]

[1]College of Nursing, Mo-Im Kim Nursing Research Institute, Yonsei University, Seoul, Korea; [2]Yonsei Evidence Based Nursing Centre of Korea: A JBI Affiliated Group, Seoul, Korea; [3]College of Nursing and Brain Korea 21 FOUR Project, Yonsei University, Seoul, Korea

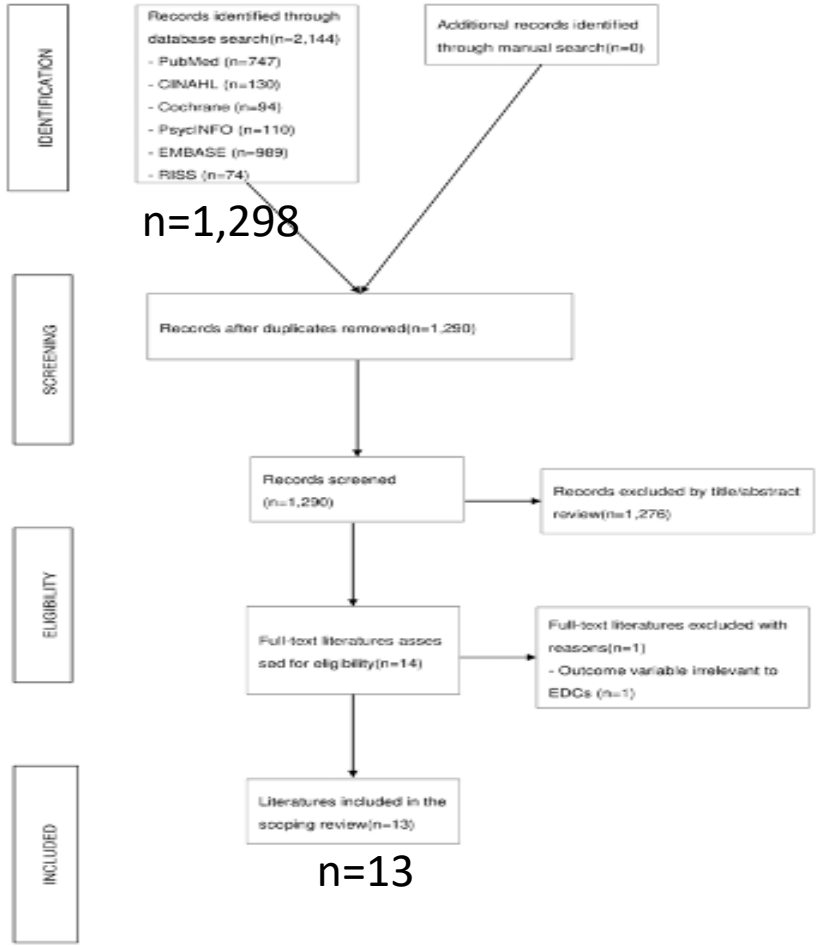
Study Inclusion Criteria:

- Provided intervention for humans regarding EDCs
- Published in English or Korean
- Were peer-reviewed

Study Exclusion Criteria:

- Cost-effectiveness on environment
- Techniques to discover/detect EDCs in bodies or materials
- Related professionals were participants

Year Published	**N (%)**
2011-2020	8 (61.54%)
2021	5 (38/46%)
Country	
U.S.	5 (38.46)
Europe	4 (30.77)
Asia	4 (30.77)



Salient Results of Park 2022 Scoping Review

- ~ 50% were single arm studies (no controls)
- Most interventions resulted in lowered EDC levels in blood and/or urine and some studies overlapped with Corbett 2022 review.
- Authors noted that compliance was challenging – e.g., most subjects didn't want to change their diet even with EDC levels demonstrated to be lower with interventions.
- 1 study revealed decreased uBPA levels and lower dysmenorrhea scores with 6 months of intervention but no control group
- 1 study revealed red Korean gensing (RKG) resulted in decreased VMS, uterine spotting, dysmenorrhea but no control group.

Park, et al. Risk management & Health Care Review ***2022;15:779-79***

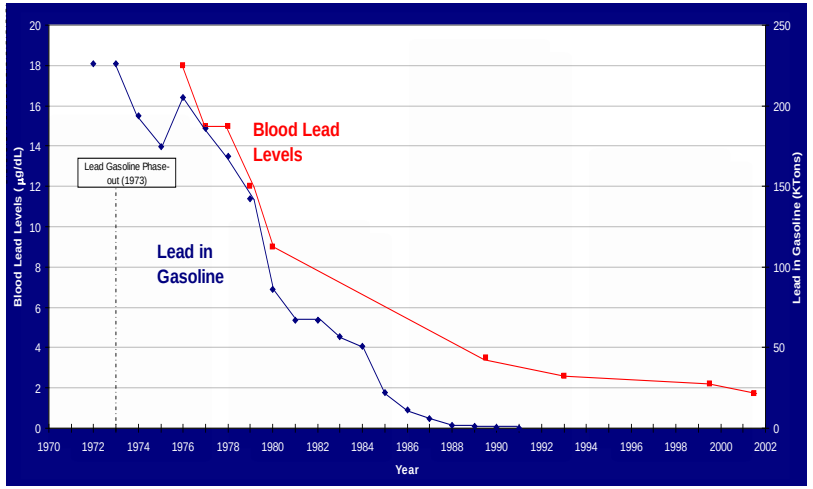
Overall Conclusions About Interventional Studies

- Most well-designed trials show benefit of lowering EDC levels (mostly 1 evaluated at a time) with interventions.
- Well-designed trials are essential to inform if interventions achieve their goals of significantly reducing EDC levels in fluids and tissues, and improvements in clinical outcomes.
- Question of patient awareness for buy in of changing behavior arises.
- Question arises if prospective interventional evidence is required before recommending some of these therapies, or, given their low side effect profiles and other benefits, whether they can be recommended based on existing observational evidence alone.

Interventions to Ameliorate EDC Effects

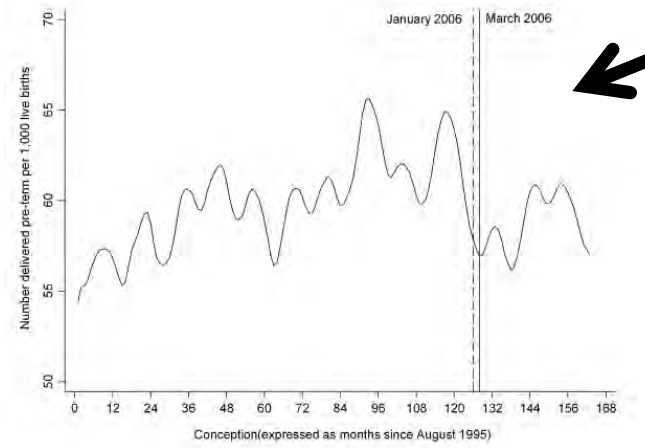
Policy Changes

Actions Can Reduce Exposures But **POLICY** Changes Are Also Needed



Removing lead from gasoline resulted in lowered blood levels at the population level over time

Preterm Births



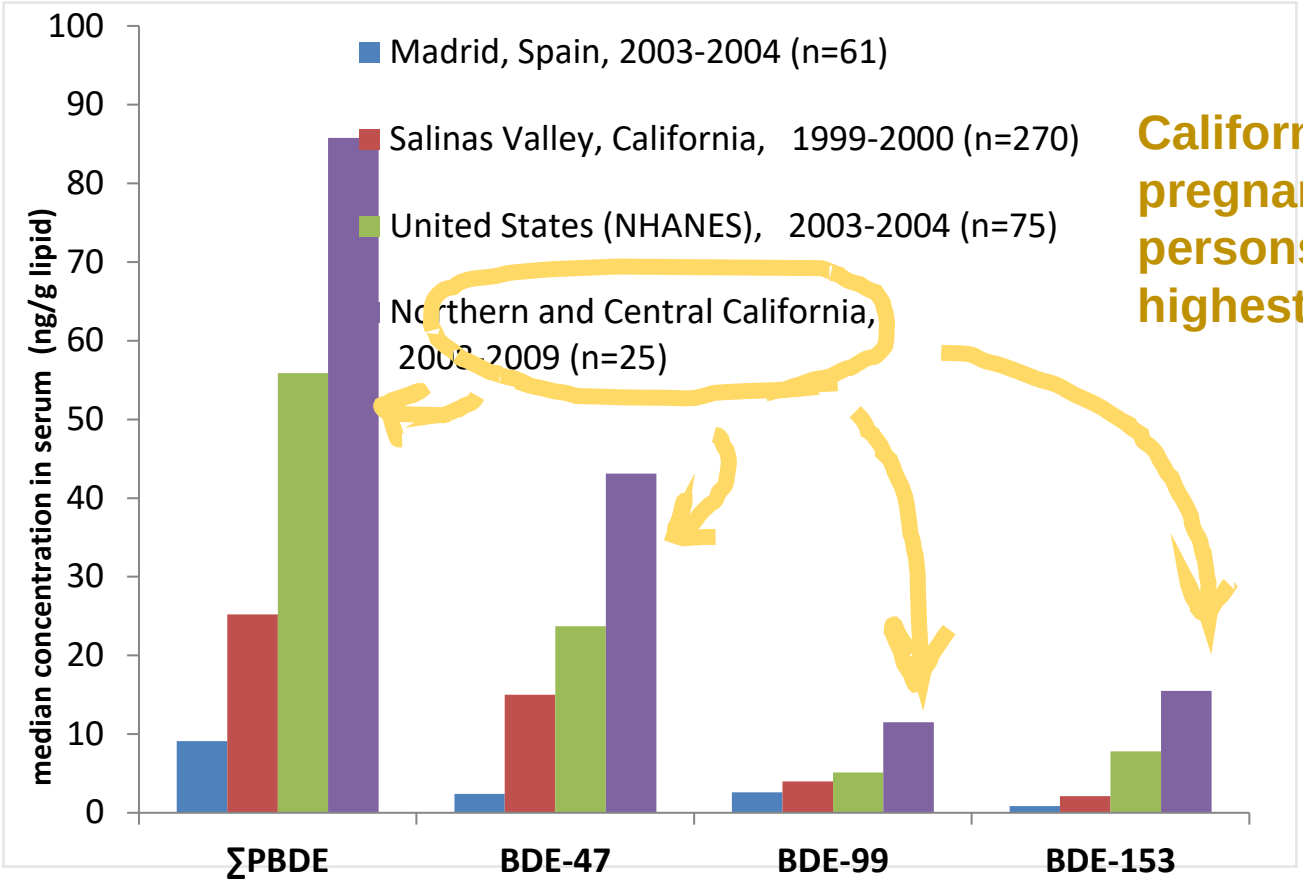
Scotland's public smoking ban

Mackay PLoS Med 2012

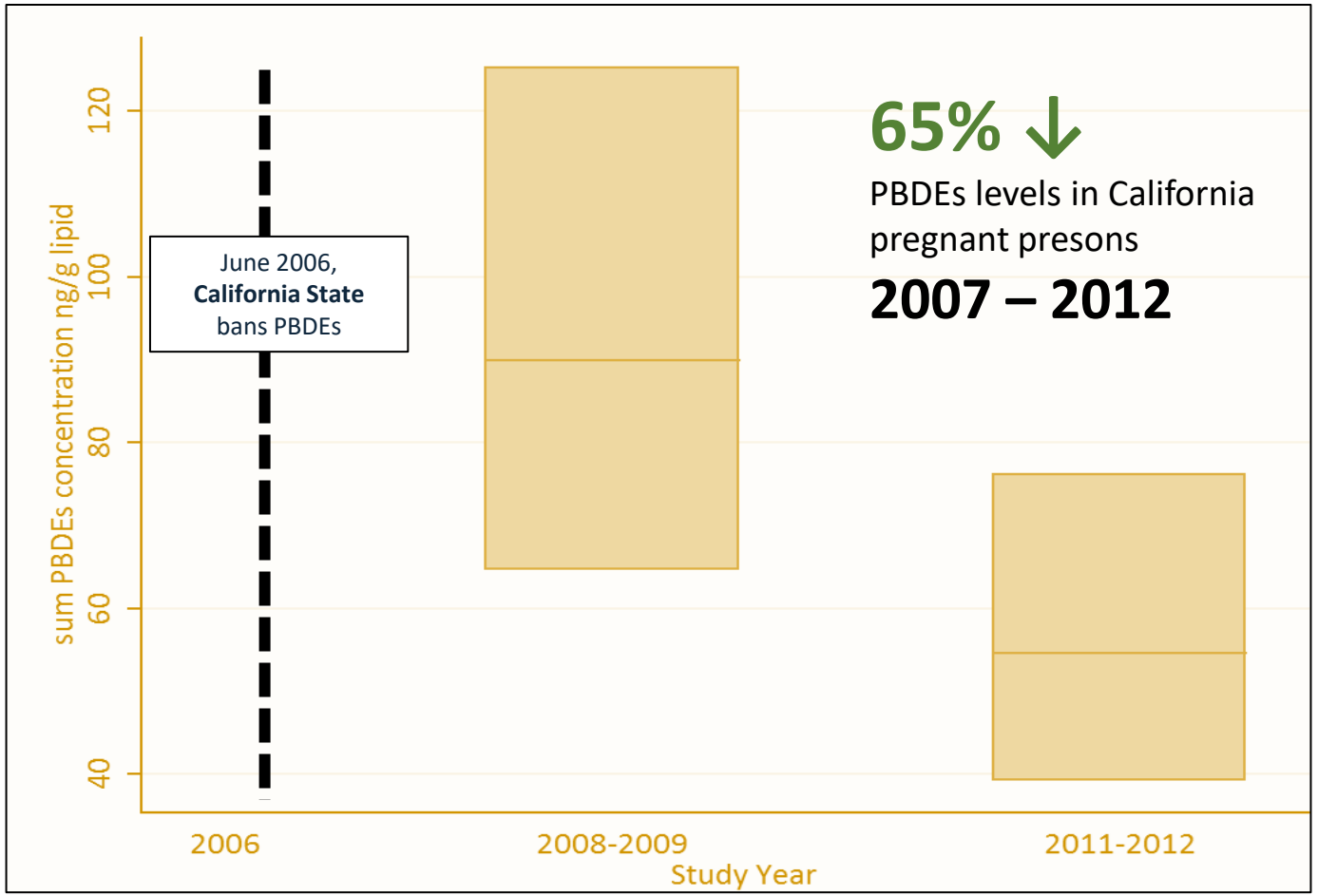
PBDEs

In humans, thyroid hormone disruption identified as possible mechanistic link
In vitro, disruption of developing fetal human brain cells
In animals, affects learning, memory, and attention
(Schreiber et al., 2010, Driscoll et al., 2008, Viberg et al. 2006)

Flame Retardants in Pregnant Persons Globally



Actions Matter – Policy
PBDEs Banned in California 2006



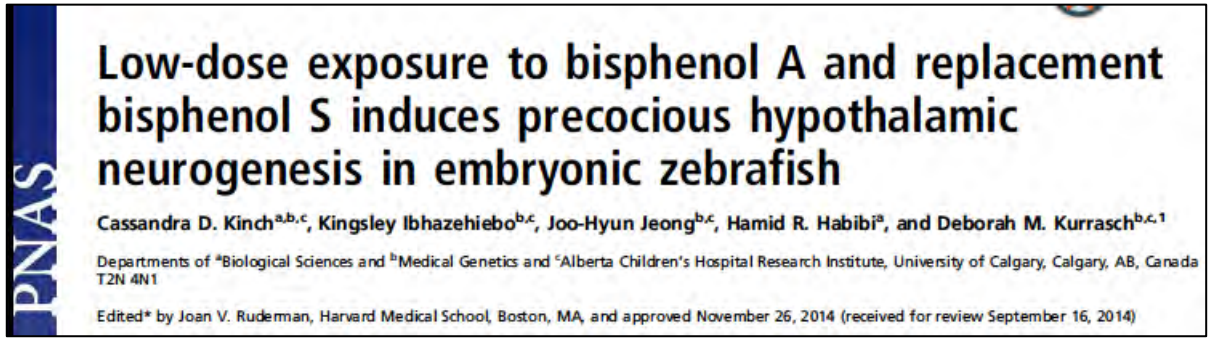
Zota A.R., et al. 2013 ES&T

Green Chemistry developed to replace hazardous chemicals, processes and make products with safer alternatives

Safer Alternatives to BPA and other EDCs?

DES → BPA → BPS and BPF

More Hormone Disruption!



PNAS

Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish

Cassandra D. Kinch[a,b,c], Kingsley Ibhazehiebo[b,c], Joo-Hyun Jeong[b,c], Hamid R. Habibi[a], and Deborah M. Kurrasch[b,c,1]

Departments of [a]Biological Sciences and [b]Medical Genetics and [c]Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada T2N 4N1

Edited* by Joan V. Ruderman, Harvard Medical School, Boston, MA, and approved November 26, 2014 (received for review September 16, 2014)

PNAS Dec 2014

A new chapter in the bisphenol A story: bisphenol S and bisphenol F are not safe alternatives to this compound

Soria Eladak, M.Sc.,[a,b,c] Tiphany Grisin, M.Sc.,[a,b,c] Delphine Moison, M.Sc.,[a,b,c] Marie-Justine Guerquin, Ph.D.,[a,b,c] Thierry N'Tumba-Byn, Ph.D.,[a,b,c] Stéphanie Pozzi-Gaudin, M.D.,[d] Alexandra Benachi, M.D., Ph.D.,[d] Gabriel Livera, Ph.D.,[a,b,c] Virginie Rouiller-Fabre, Ph.D.,[a,b,c] and René Habert, Ph.D.[a,b,c]

[a] Unit of Genetic Stability, Stem Cells, and Radiation, Laboratory of Development of the Gonads, Université Paris Diderot, Sorbonne Paris Cité, Fontenay-aux-Roses; [b] Commissariat à l'Energie Atomique, Fontenay-aux-Roses; [c] Institut National de la Santé et de la Recherche Médicale, Unité 967, Fontenay-aux-Roses; and [d] Service de Gynécologie-Obstétrique et Médecine de la Reproduction, Hôpital A. Béclère, Université Paris Sud, Clamart, France

Fertil Steril 2015;103:11-21

How do we identify those at risk of harm from EDCs and counsel them to mitigate/minimize their risks?

Do HCPs Do An Environmental History?

American Congress of Obstetricians and Gynecologists Survey (ACOG) (N=2514)

78%

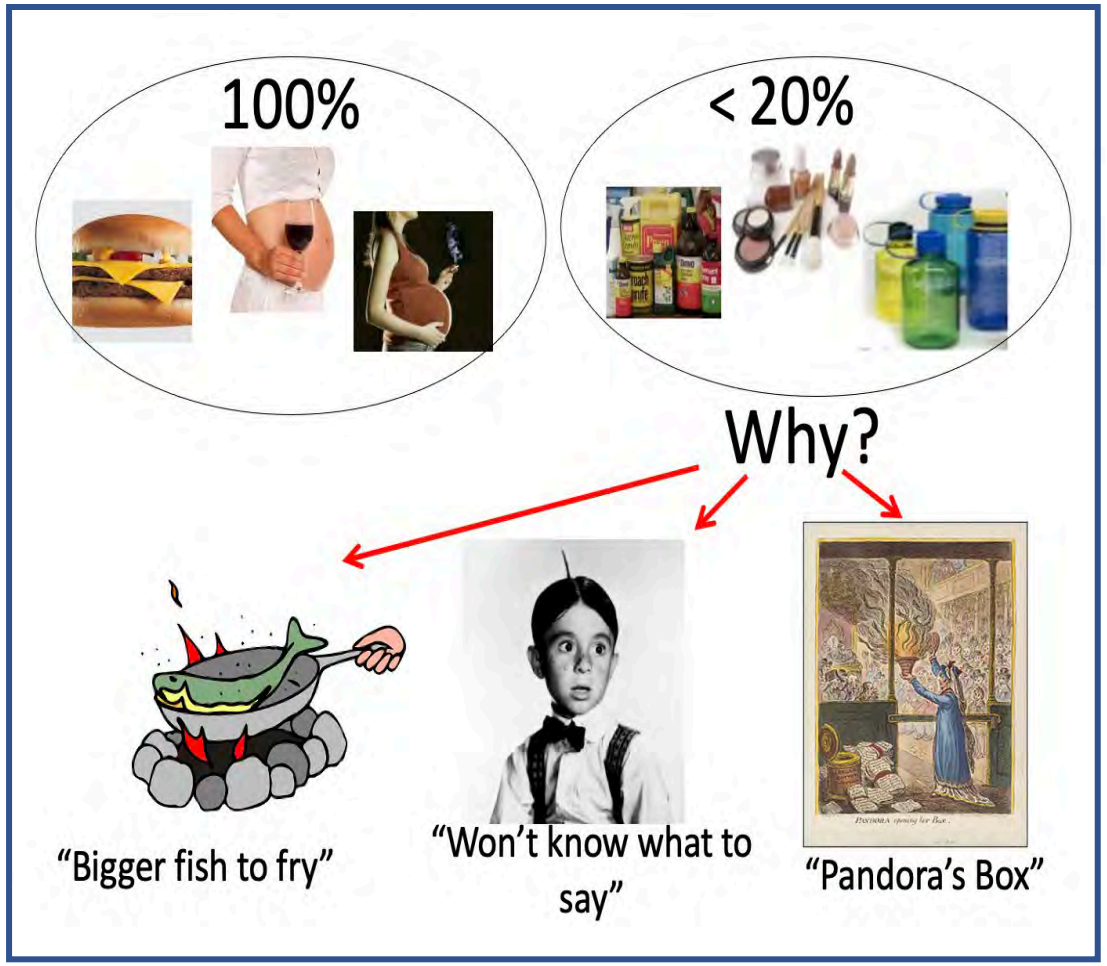
of obstetricians surveyed feel they can reduce patient exposure

Yet…..

<25% report they take an environmental health history

Stotland NE, Sutton P, Trowbridge J, Atchley DS, Conry J, et al. Counseling Patients on Preventing Prenatal Environmental Exposures - A Mixed-Methods Study of Obstetricians. PLoS ONE 2014;9(6): e98771. doi:10.1371/journal.pone.0098771

What Do Obstetricians Ask About and Interventions at Point of Care



Interventions:

(1) brochures to patients on PNC entry or making available in waiting or exam rooms

(2) staff providing patients with information on nutritional counseling or other germane health education regarding avoidance of toxic chemicals

(3) Taking an environmental health history – smart sets in EHR

Role of the HealthCare Team to Promote Successful Intervention Strategies

Taking an Exposure History

Examples are available at
http://prhe.ucsf.edu/clinical-practice-resources;
https://www.atsdr.cdc.gov/hec/csem/exphistory/docs/exposure_history.pdf

When counseling patients about their exposures, HCPs need to:

- **Understand patient risk is a function of** toxicity, dose, frequency, duration, and timing of exposures (especially vulnerable developmental windows, and individual patient vulnerability – e.g., underlying health conditions, SDS) and exposure routes.

- **Identify patients with hazardous occupations or hobbies**. Persons with occupational/recreational toxic exposures are at high risk of adverse reproductive outcomes.
  - Legal workplace limits are not created to protect pregnant persons.
  - Persons exposed to chemicals via hobbies have lower exposures vs working in similar industries (e.g., jewelry making), but may have less safety training.

Giudice et al. Environmental factors in reproduction, In: Reproductive Endocrinology, Yen, Jaffe, Barbieri, Williams, Strauss, Elsevier, Boston, 2023

What Do Individuals Know About EDCs?

Qualitative studies show knowledge and awareness of EDCs among lay public is low.

Male infertility: Maxim *J. Risk Res.* **2013**, *16*, 677–695
- Perceptions about controversial link between exposure to EDCs and a decline in human male fertility was well received, contradicting assumptions that transparency about scientific uncertainty of EDCs elicits negative psychological effects

Pregnant persons: *Rouillon Int. J. Environ. Res. Public Health **2017**;14:1021. **2018**;15:2231.*
- Did not believe they were particularly susceptible to exposures but believed exposures to EDCs were extremely dangerous.

General public*: Kelley, Int J Environ Res Public Health. **2020**;17:7778*
- 19-65 yo in focus groups (n=34) in Belfast.
- Generally, little knowledge of and awareness about EDCs, their sources and associated health effects.
- While unaware of possible individual mitigation strategies, the majority expressed government responsibility to mitigate effects.

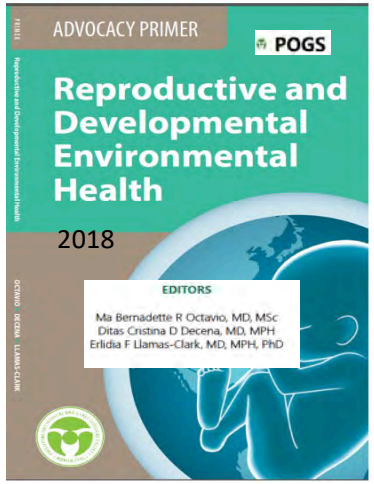
How Can HCPs Promote Successful Intervention Strategies?

- HCPs should take an exposure history and provide patients with resources and referrals.
- Need to get information to patients about known effects and reducing/eliminating exposures to EDCs with extrapolation to preventing adverse health impacts.
- HCPs can work with community leaders and policy officials to expand the network of information, without being topic experts themselves.
- Government and academic resources and referrals re specific environmental exposures and reproduction are available.

Giudice et al. Environmental factors in reproduction, In: Reproductive Endocrinology, editors Yen, Jaffe, Barbieri, Williams, Strauss, Elsevier, Boston, 2023

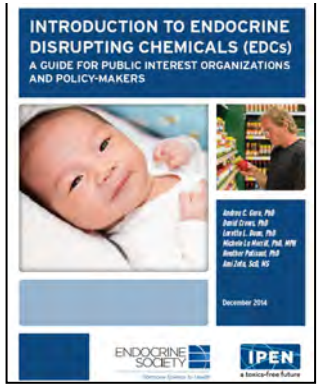
Some Resources to Reduce Toxic EDC Exposures

Educate and Advocate



FIGO
International Federation of Gynecology and Obstetrics
the Global Voice for Women's Health

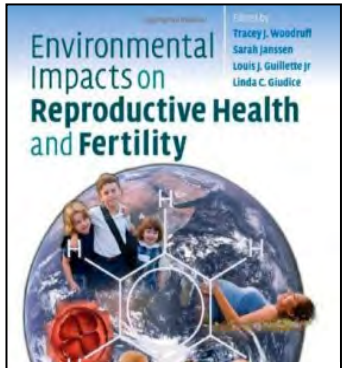
EDC-2: 2015
Gore et al



ACOG 2022 Updated Committee Opinion on Environment and Climate Impacts on Women's Health.

ACOG
The American College of Obstetricians and Gynecologists

Policy Priorities Environmental Health



Woodruff T, Jansen S, Guillette, L, Giudice LC 2008

asrm
American Society for Reproductive Medicine

Environment & Reproduction Special Interest Group

Project TENDR

ACOG
The American College of Obstetricians and Gynecologists

IFFS

Avoiding Toxic Chemicals *BEFORE*, *DURING* and *AFTER* Pregnancy

Some specifics

10 Tips for a Healthier Pregnancy

1. Avoid eating, drinking or storing food in plastic
2. Don't microwave in plastic
3. Cook with cast iron or stainless steel not non-stick pans
4. Avoid eating fish high in Hg or PCBs
5. Eat fresh, organic foods, or clean off pesticides
6. Limit cosmetics
7. Avoid dry cleaning or stain treating clothing
8. Use a wet mop when cleaning
9. Avoid consumer products with flame retardants
10. Remove shoes before entering your home.

FIGO Committee on Climate Change and Toxic Environmental Exposures

FIGO.ORG
English, Spanish, French

POLICY EFFORTS

- Need:
  - transparency of data
  - population educated in risks associated with specific exposures
  - informed governing body and industry partners with the common will to change policy in the interest of the public health.

- Disparities in exposure risks among vulnerable populations mandate inclusion of environmental justice in policies to improve the public health.

- Chemical regulations differ widely across the globe.
  - The **Reach** (Registration, Evaluation, Authorisation and Restriction of Chemicals) policy addresses production and use of chemicals and impacts on human health and the environment, with the onus on the manufacturer to demonstrate safety to keep their chemicals in the marketplace.
  - In the **US chemicals** released into the marketplace fall short of the scrutiny is suspected or demonstrated

We have some work to do……

Kassotis CD, Vandenberg LN, Demeneix BA, Porta M, Slama R, Trasande L. Endocrine-disrupting chemicals: economic, regulatory, and policy implications. Lancet Diabetes Endocrinol. 2020;8:719; . Giudice LC. Environmental impact on reproductive health and risk mitigating strategies. Current Opinion Obstet Gynecol. 2021 08(01); 33:343-349

CONCLUSIONS

www.prhe.ucsf.edu

- Scientific and epidemiologic data reveal mechanisms and associations of preconception, prenatal and adult exposures to EDCs negatively impacting women's health and developmental processes and outcomes.
- While strategies to control EDC exposures may show lower body burdens, whether there is ***direct improvement*** of epidemiologically associated disorders is largely unproven but should not derail preventive strategies.
- While EDCs are ubiquitous, highest risk is among vulnerable populations, who should be included in all intervention mitigation strategies.
- We need to incorporate environmental and occupational health in professional education.
- Health care professionals, scientists, citizens can play a major role in raising awareness among colleagues, trainees, patients, the general public, and government leaders - key to improving human health.

Giudice et al. Environmental factors in reproduction, In: Reproductive Endocrinology, editors: Yen, Jaffe, Barbieri, Williams, Strauss, Elsevier, Boston, 2023

Environmental Toxicants Are Tilting the Risk Balance Unfavorably for Women's Health Outcomes

This is an **environmental issue**, a **public health issue**, an **occupational health issue**, a **social justice issue**, a **human rights issue**, an **economic issue**, a **political issue**, and a **gender issue**.

Thank you

Advancing Health Equity

Tamarra M. James-Todd, MPH, Ph.D., Tonya Sharmaine Lane, M.S.

Moderated by LT Abayomi Walker

Advancing Health Equity

Tamarra James-Todd, PhD, MPH

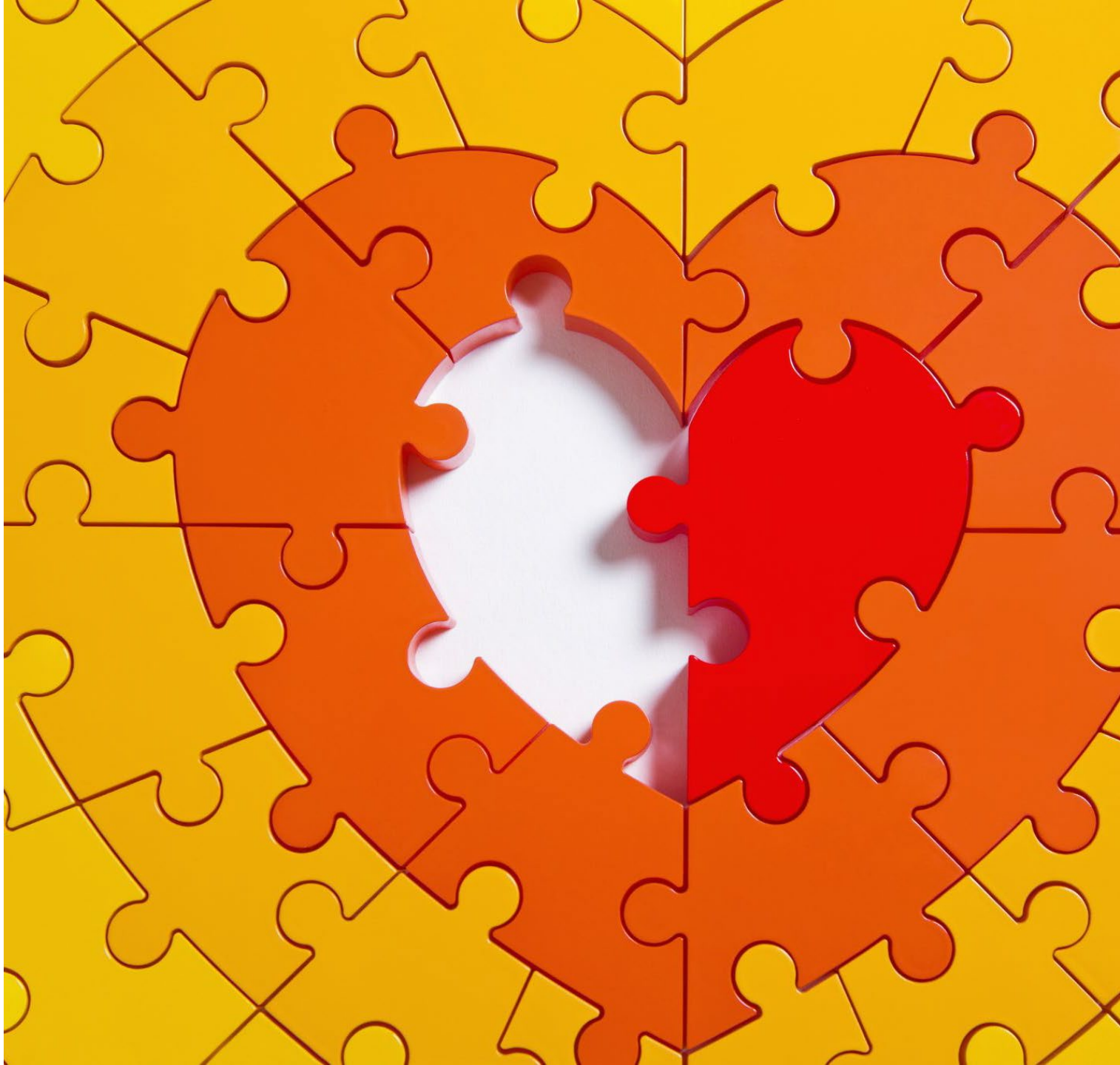
Associate Professor of Environmental Reproductive Epidemiology, Director, Environmental Reproductive Justice Lab

Harvard T.H. Chan School of Public Health

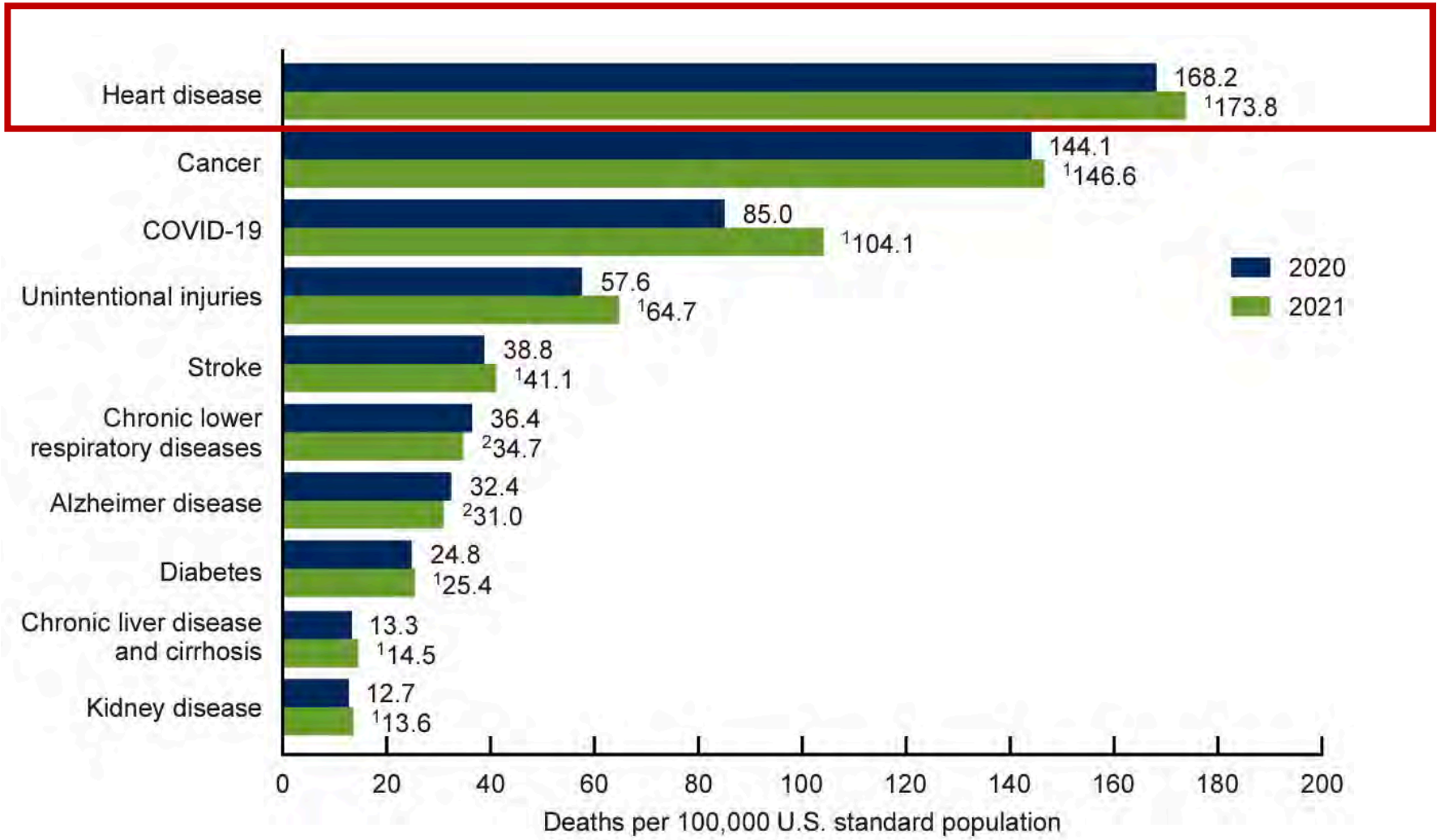
Racial/ethnic disparities in endocrine disrupting chemical exposures and disparities in chronic disease risk

Tamarra James-Todd, PhD, MPH
Mark and Catherine Winkler Associate Professor of Environmental Reproductive Epidemiology
Harvard T.H. Chan School of Public Health
Director, Environmental Reproductive Justice Lab

July 19, 2023



Age-adjusted mortality rate for 10 leading causes of death in U.S., 2020 and 2021



National Center for Health Statistics, National Vital Statistics System, Mortality

Health across the life course: examples of cardiovascular disease risk factors

Prenatal | Infancy | Childhood | Adolescence/ Young Adulthood | Reproductive years | Postmenopausal/ Older age

-Intrauterine growth restriction
-GDM or preeclampsia

-Rapid catch-up growth
-LGA

-Early menarche
-Obesity

-Pregnancy loss
-Pregnancy complications

-Early menopause
-Hot flash severity

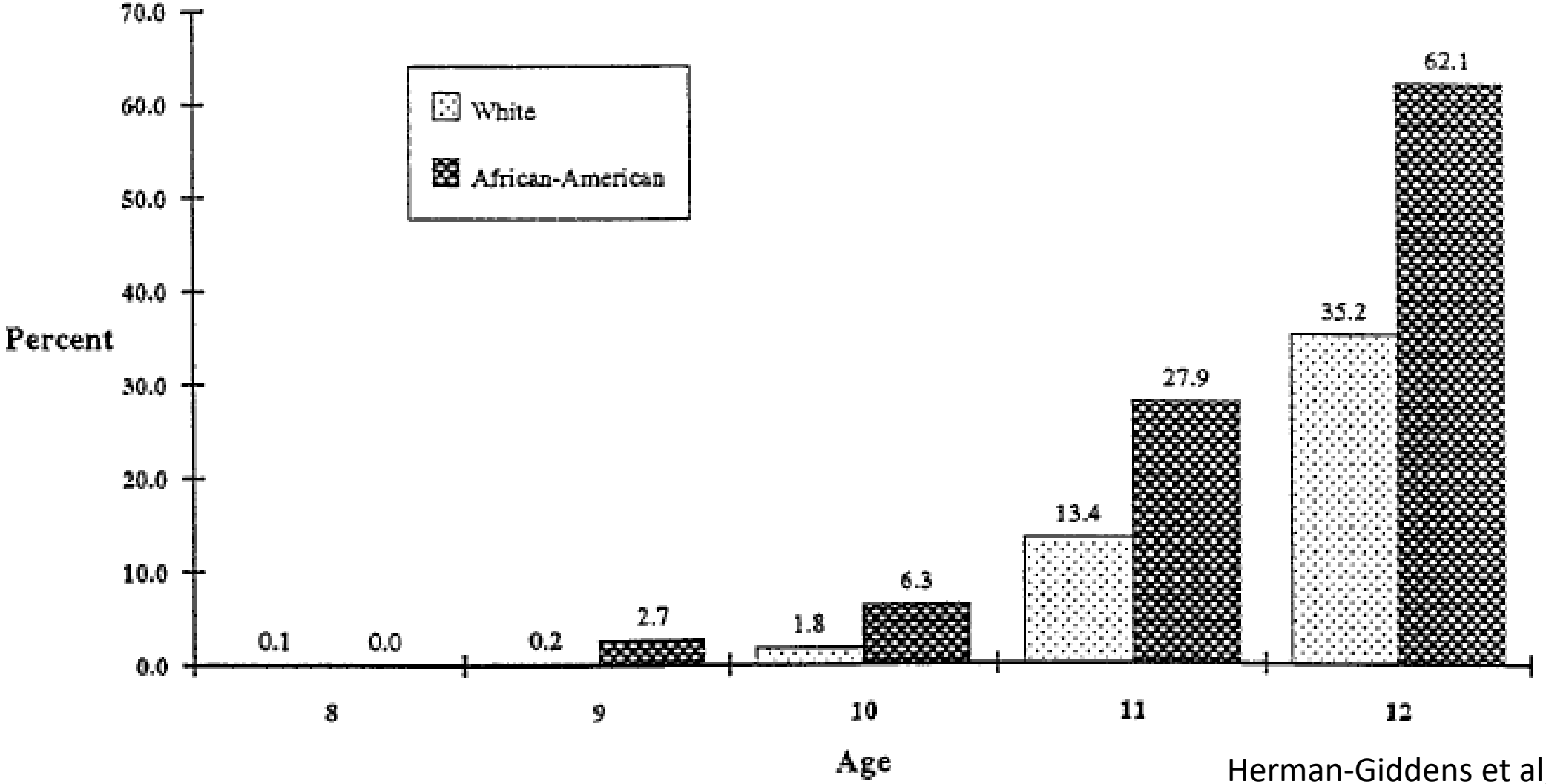
-Hypertension, dyslipidemia, diabetes, obesity, PCOS

FIGURE 1

Hypertension Prevalence by Sex and Race/Ethnicity

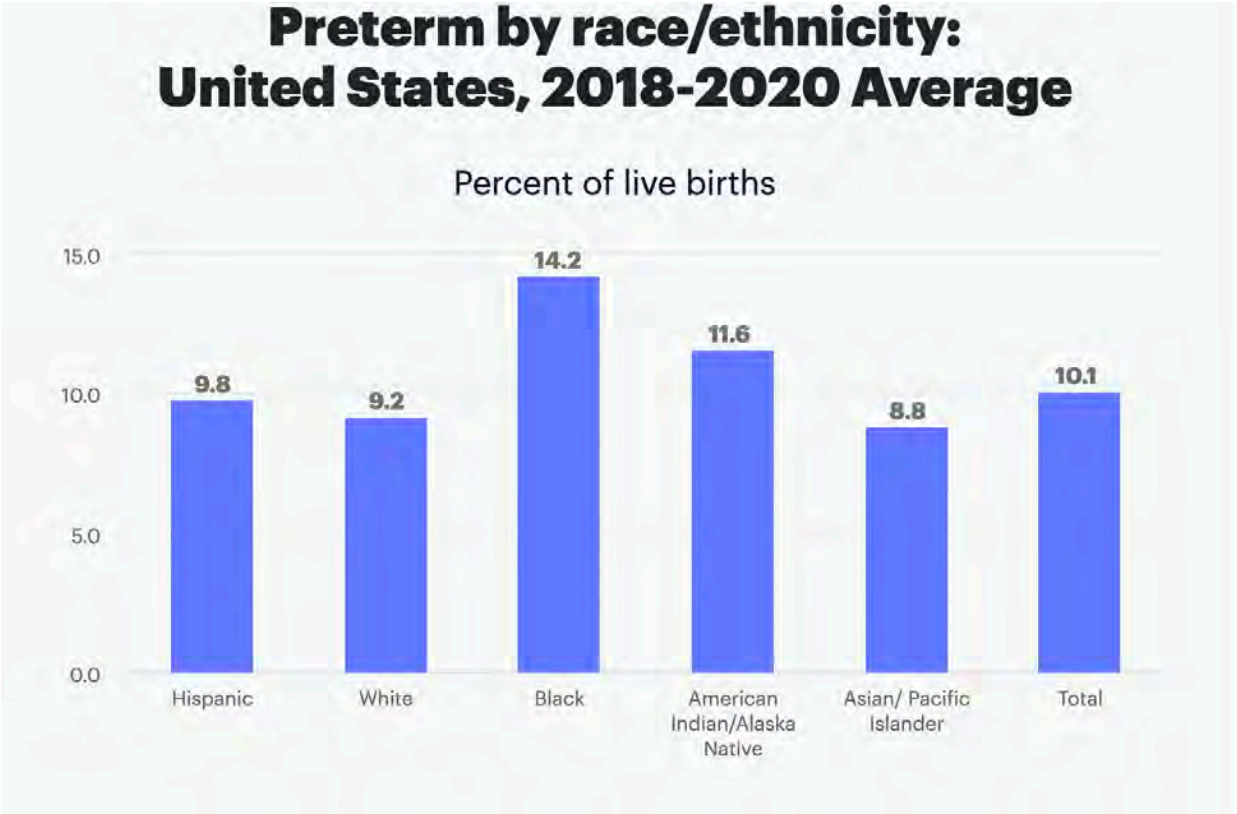
Source: Yoon SS, Fryar CD, Carroll MD. Hypertension prevalence and control among adults: United States, 2011–2014. NCHS data brief, no 220. Hyattsville, MD: National Center for Health Statistics. 2015.

Racial disparities in cardiovascular disease risk factors across the life course: early menarche

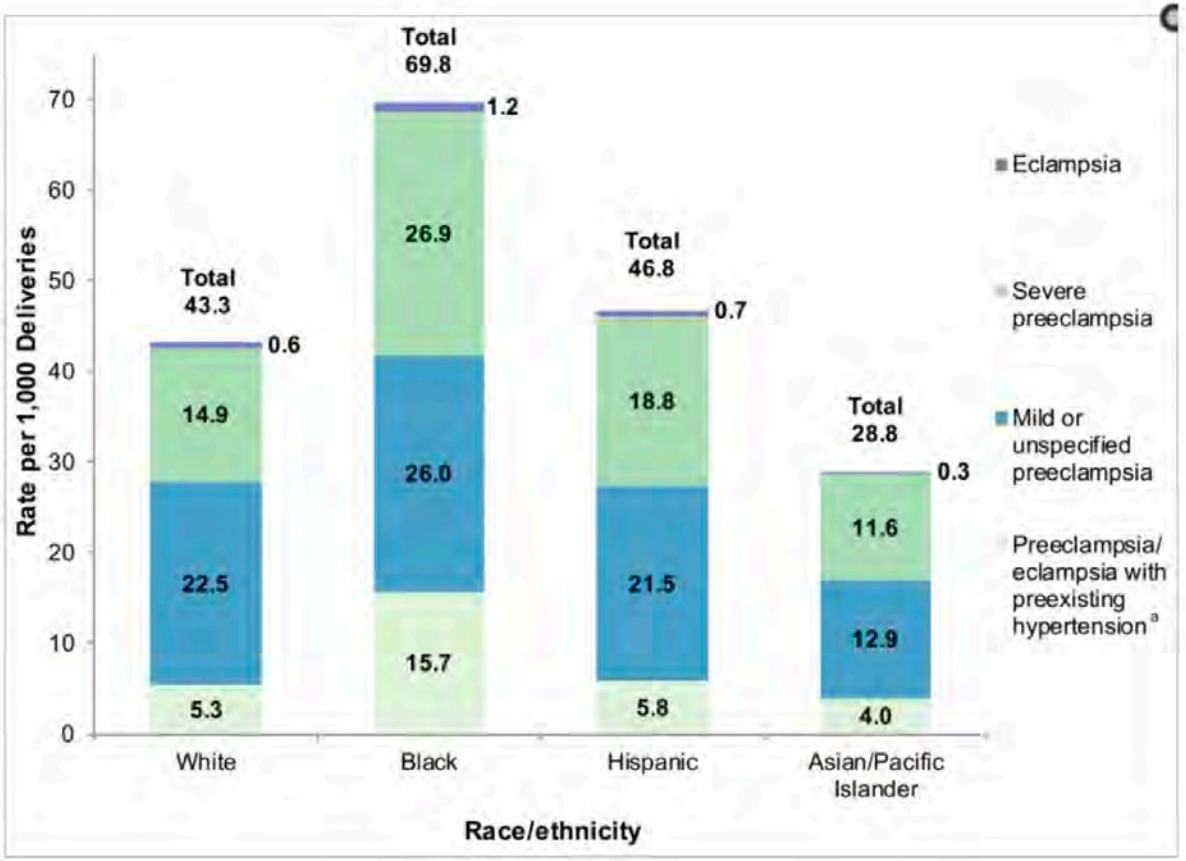


Herman-Giddens et al, Pediatrics 1997

Racial disparities in cardiovascular disease risk factors across the life course: pregnancy complications



March of Dimes 2022



Fingar KR et al, HCUP Stat Brief 2017

Racial disparities in cardiovascular disease risk factors across the life course: menopause

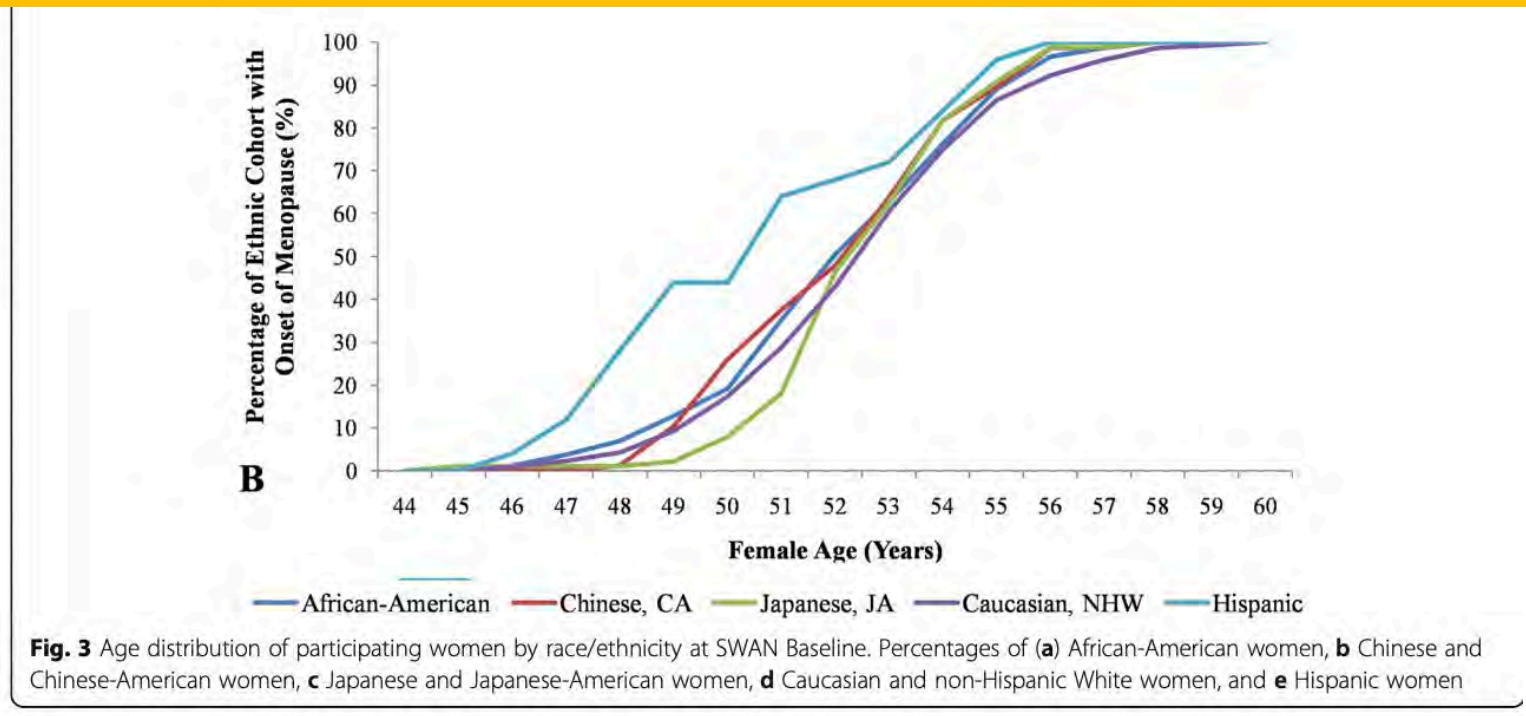
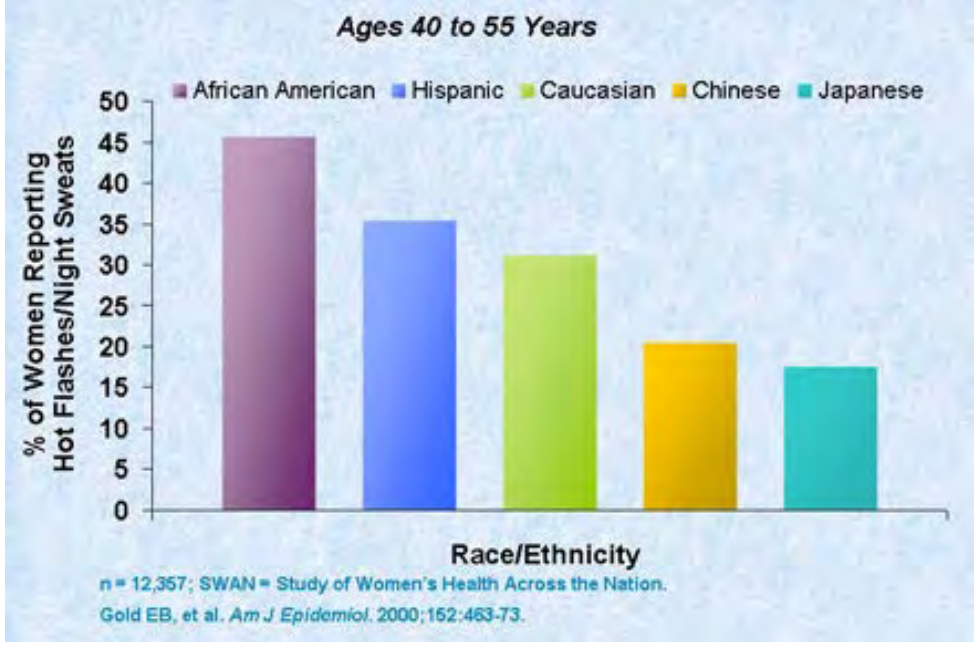


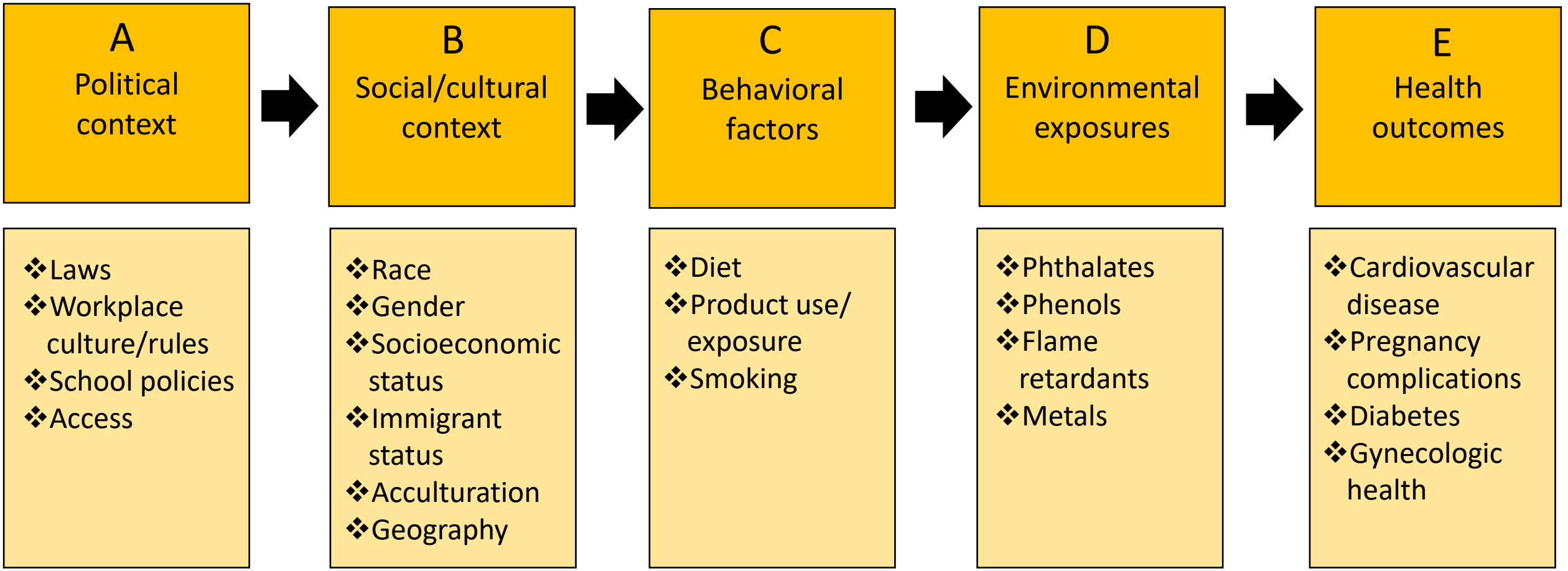
Fig. 3 Age distribution of participating women by race/ethnicity at SWAN Baseline. Percentages of (**a**) African-American women, **b** Chinese and Chinese-American women, **c** Japanese and Japanese-American women, **d** Caucasian and non-Hispanic White women, and **e** Hispanic women

Chan et al, BMC Women's Health 2020



Gold EB et al, Am J Epi, 2000

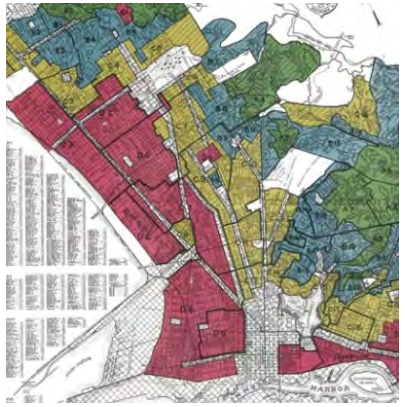
Translational Epidemiologic Approach to Health Disparities



Bellavia et al, Environ Epidemiol, 2018

Translational Epidemiologic Approach to Health Disparities

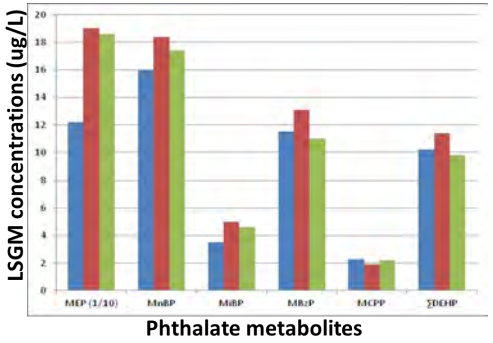
A Political context → **B** Social/cultural context → **C** Behavioral factors → **D** Environmental exposures → **E** Health outcomes



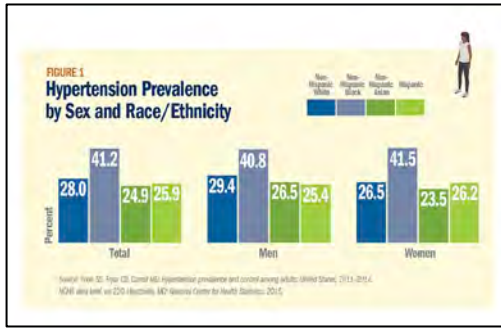
Historic redlining

Racial differences in wealth

Safer product and food apartheid

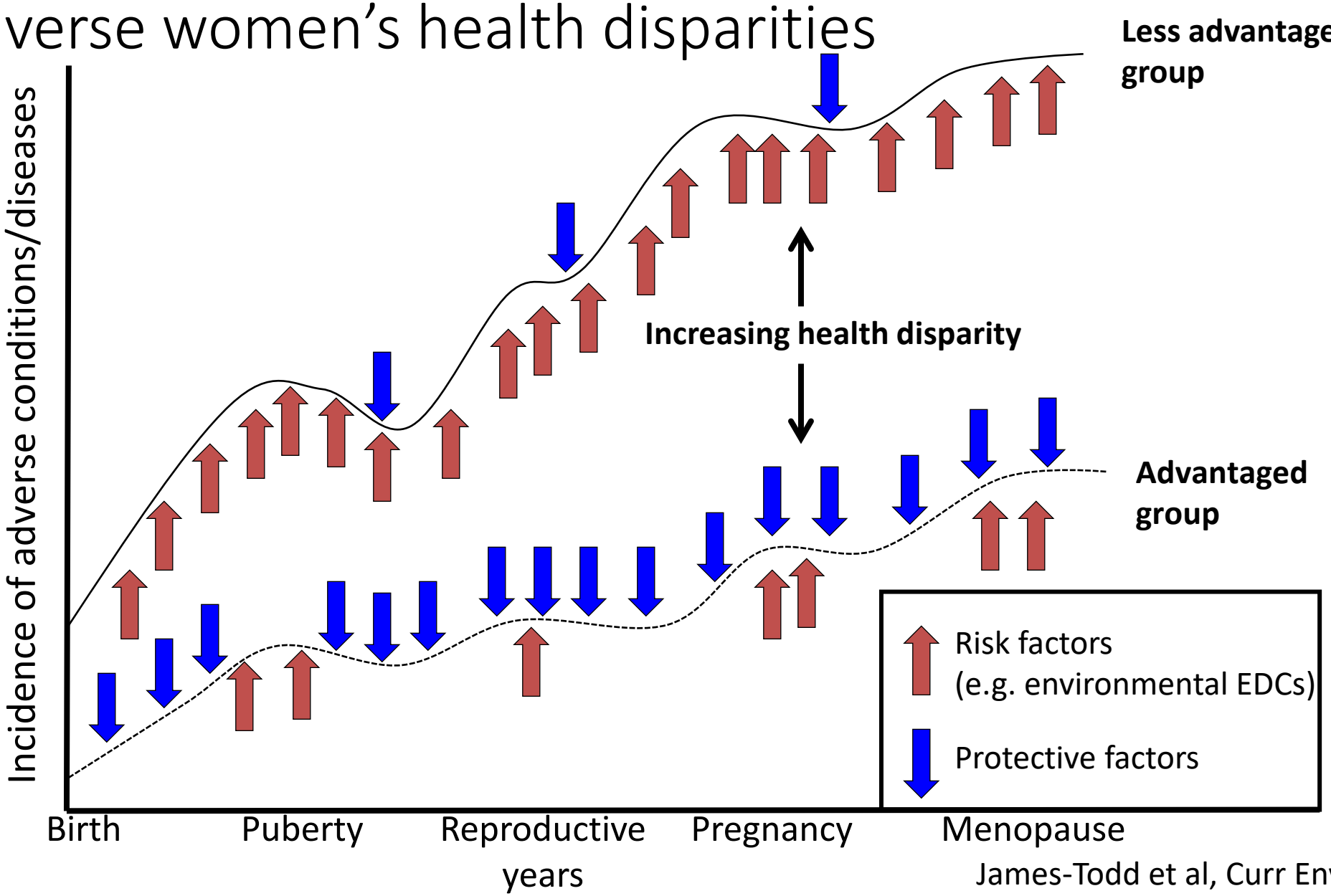


Disparities in EDCs



Health disparities

Contribution of unequal environmental exposures to increasing risk of adverse women's health disparities



James-Todd et al, Curr Env Hlth Rep 2016

Endocrine Disrupting Chemicals in Consumer Products

Pesticides

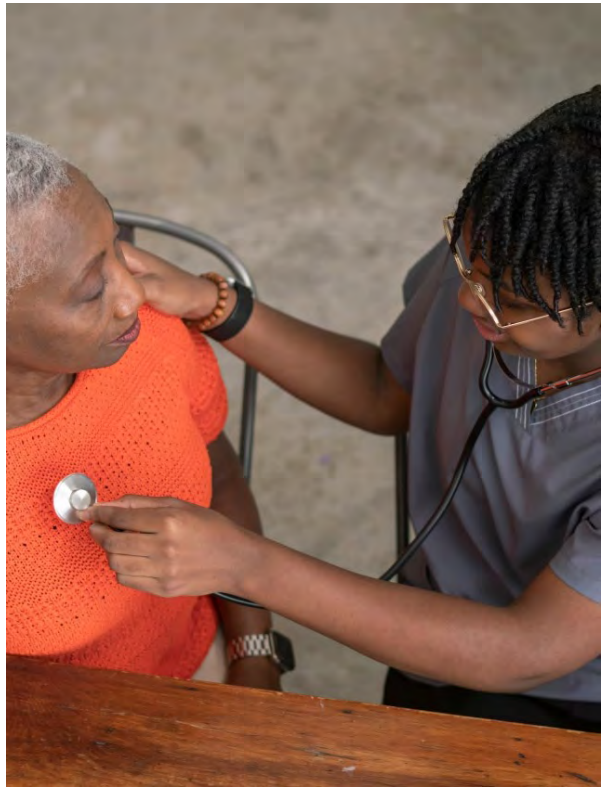
Plasticizers

Surfactants

Phenols

Flame retardants



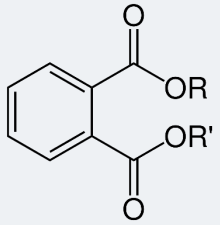



Two examples:

1. Phthalates and cardiovascular disease risk

2. PFAS and cardiovascular disease risk

Examples of Disparities in Environmental Chemical Exposures

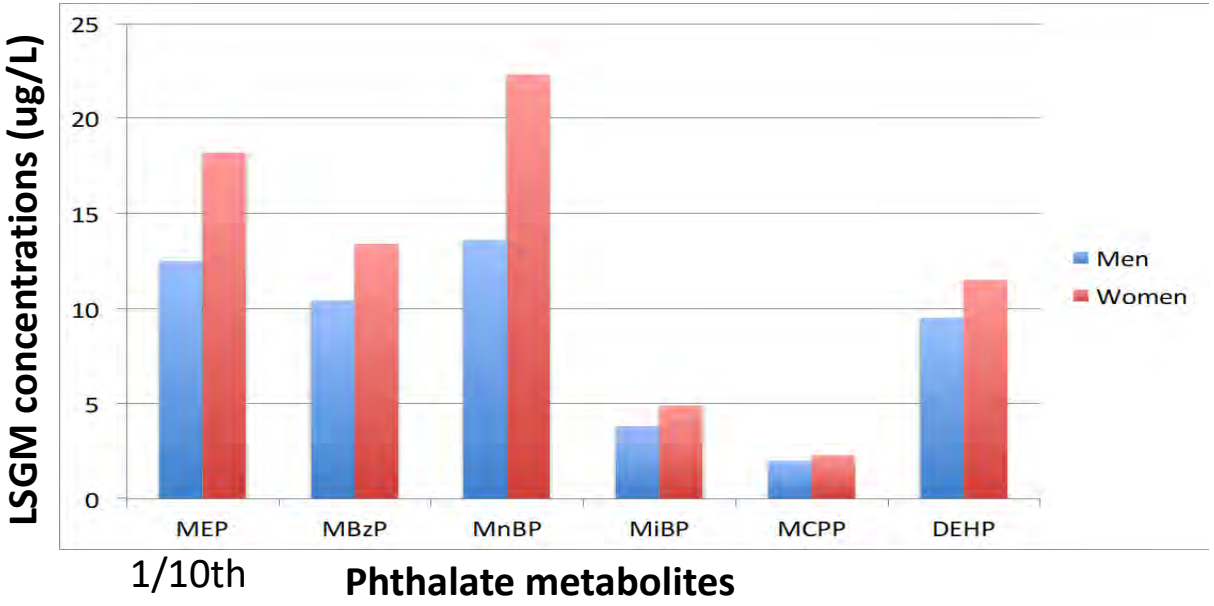


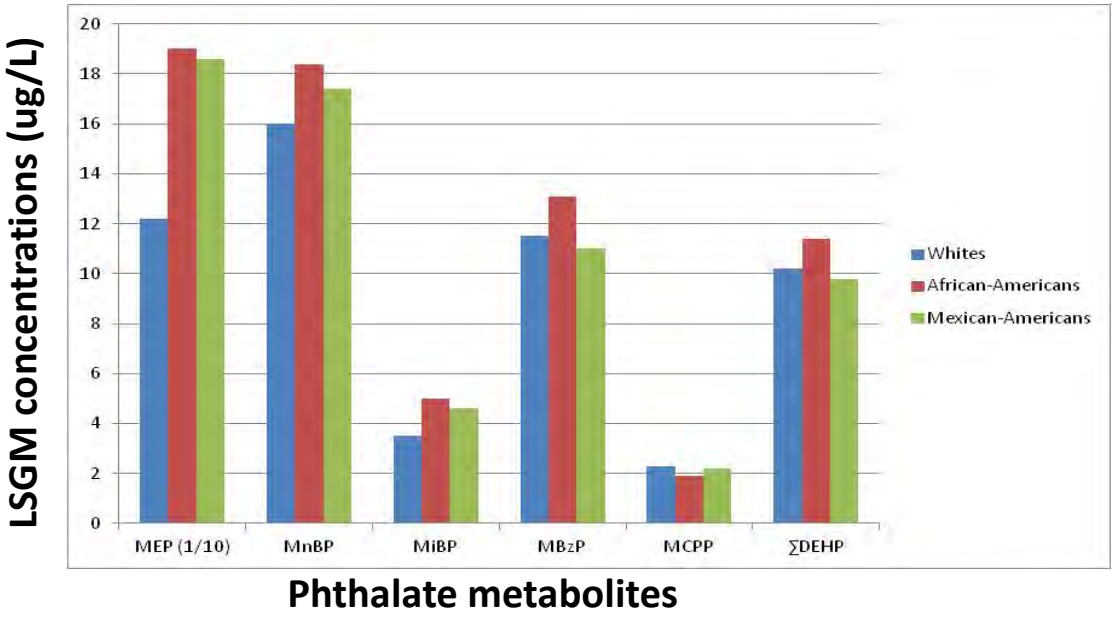
Phthalates

Examples:

- ❖ Personal care products
- ❖ Diet/food packaging
- ❖ Medical tubing/medication/plastics

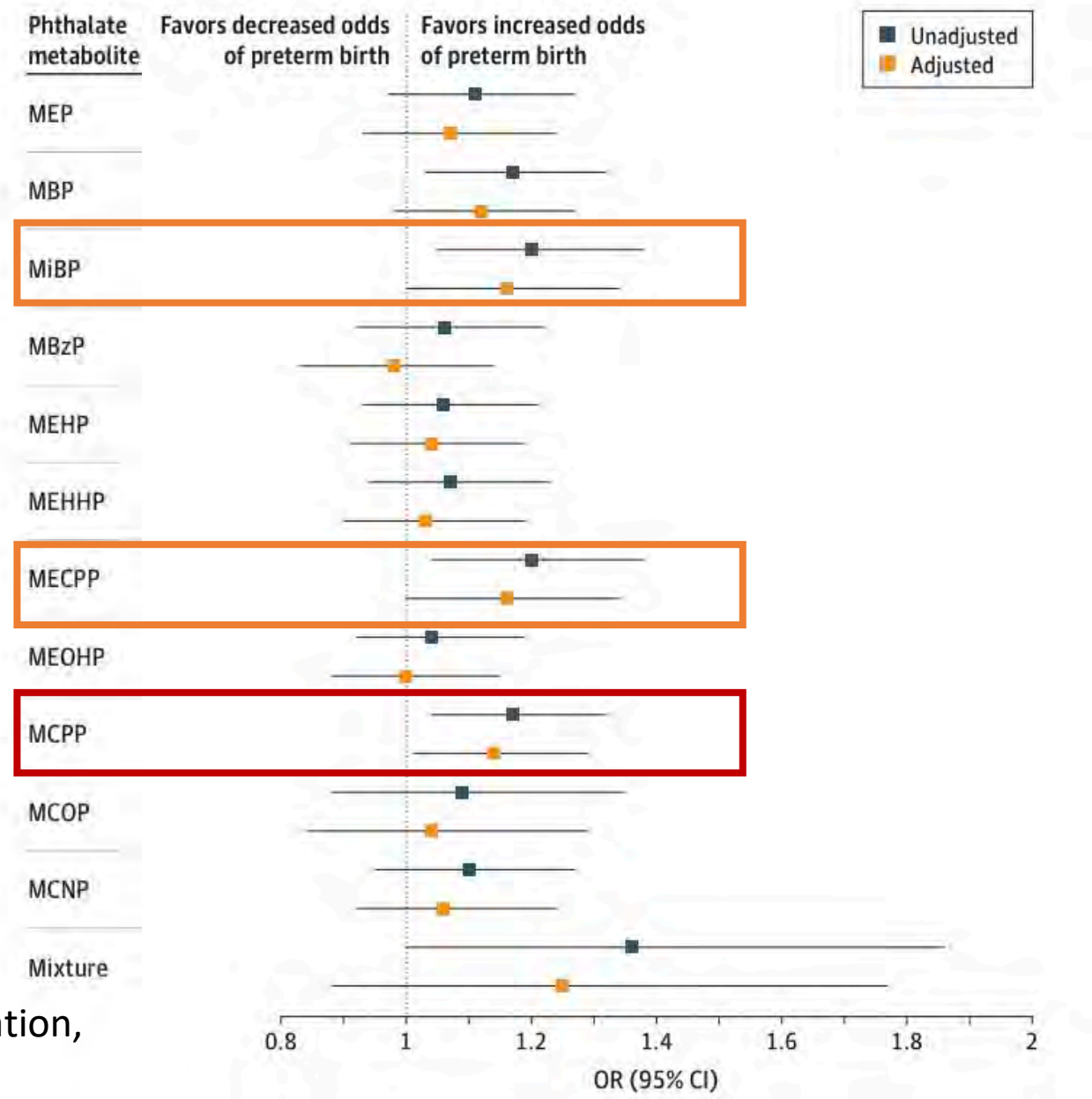
NHANES 2001-2008





James-Todd et al, Environ Health, 2014

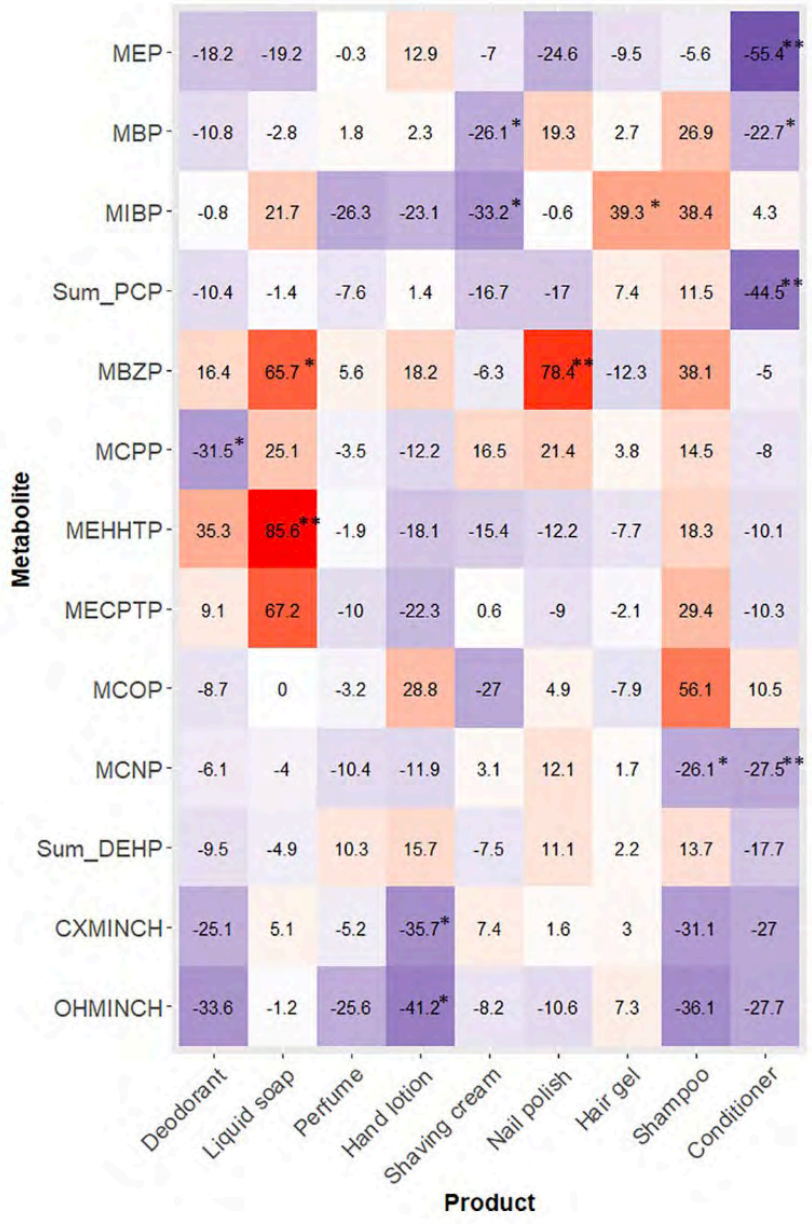
Phthalates and preterm birth

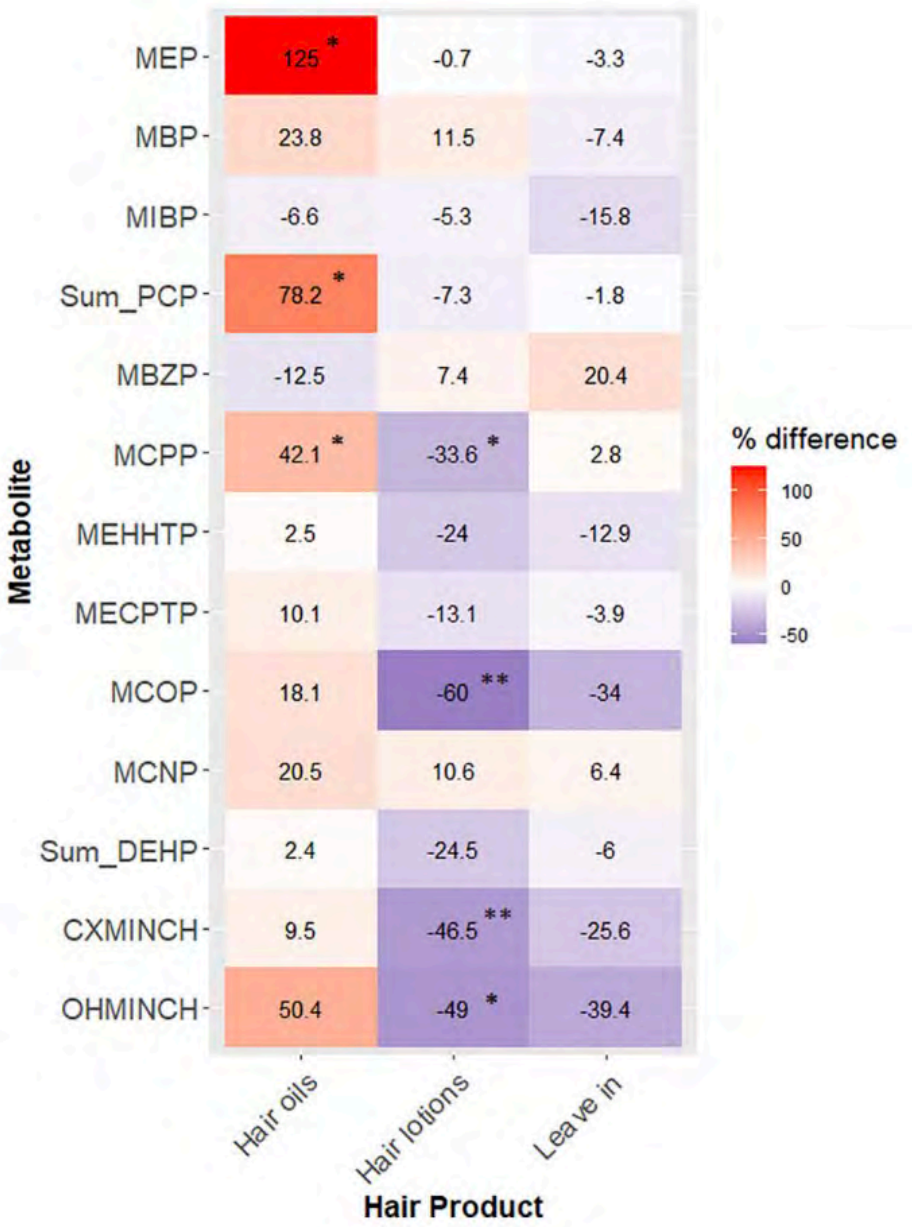


Adjusted for maternal age, race/ethnicity, education, and pre-pregnancy body mass index

Welch et al, JAMA Pediatr 2022

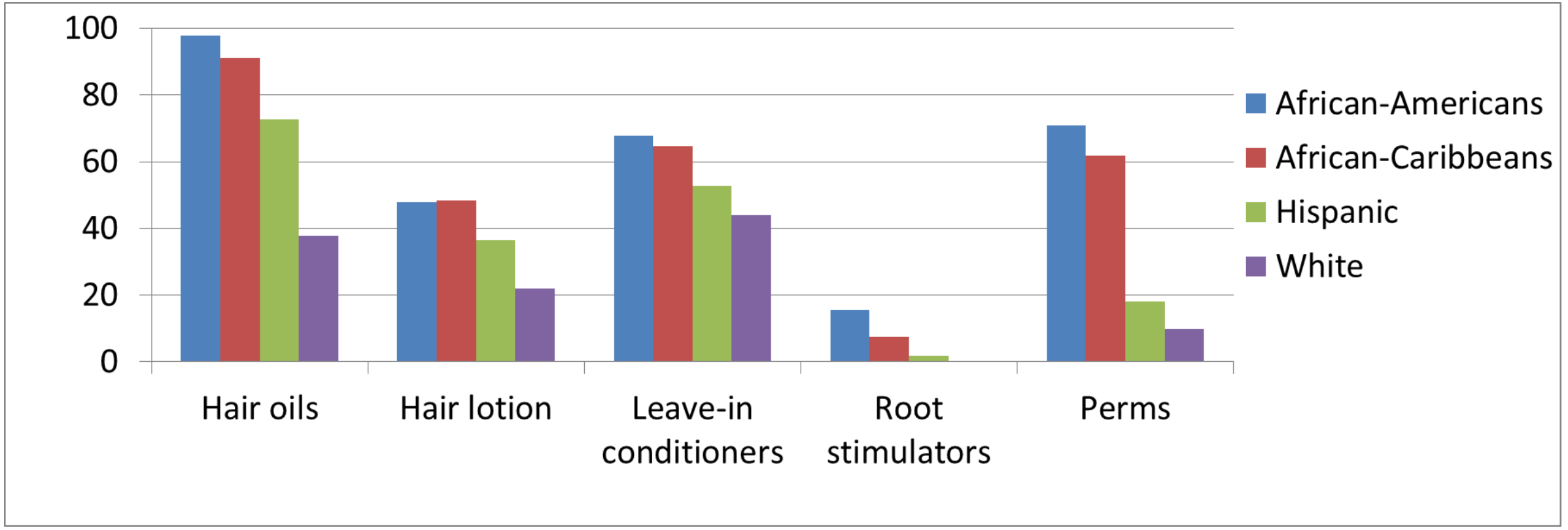
Product use and phthalate metabolite concentrations





Fruh et al, STOTEN 2022

Association between Race/Ethnicity and Hair Product Use



James-Todd, J Immigr Minor Health. 2012

Association between Hair Product Use and Preterm Birth:

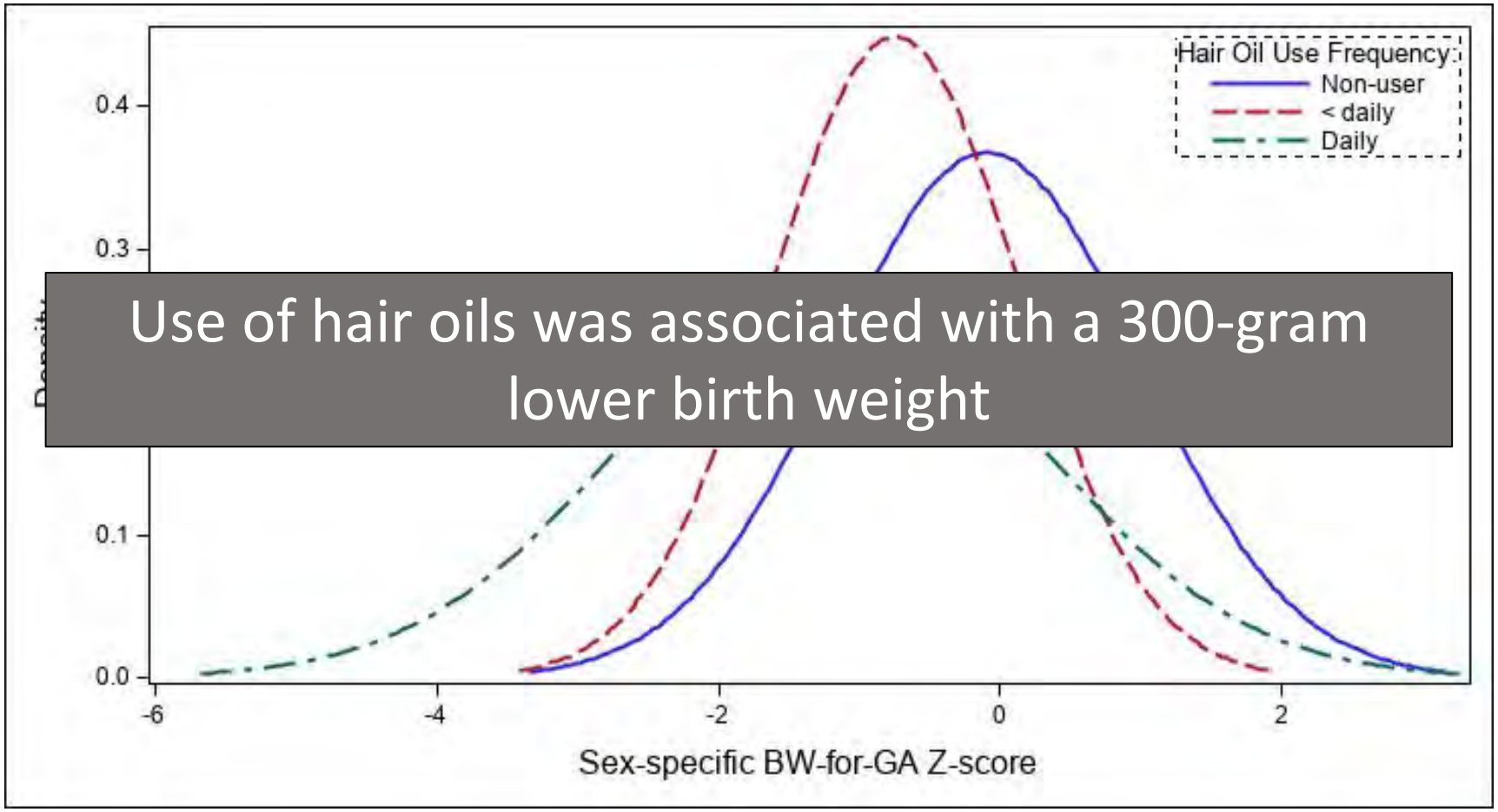
Visit Time Point	Hair oil use	Hair lotion use	Leave-in conditioner use
Visit 1			
Daily	-5.8 (-16.3, 4.7)	3.1 (-10.7, 16.9)	5.1 (-5.3, 15.6)
<Daily	0.5 (-6.7, 7.7)	-3.8 (-10.7, 3.2)	1.7 (-4.8, 8.2)
Never	Ref.	Ref.	Ref.
Visit 2			
Visit 3			
Daily	-1.0 (-6.7 4.6)	1.7 (-5.4, 8.7)	-2.5 (-11.5, 6.5)
<Daily	-1.3 (-7.0, 4.5)	-2.3 (-8.0, 3.5)	-2.5 (-7.1, 2.2)
Never	Ref.	Ref.	Ref.
Visit 4			
Daily	-8.3 (-14.9, -1.6)	-1.8 (-12.6, 9.0)	-2.1 (-9.6, 5.4)
<Daily	0.9 (-3.8, 5.7)	-3.0 (-9.0, 3.0)	-0.4 (-5.0, 4.3)
Never	Ref.	Ref.	Ref.

Daily use of hair oils in late pregnancy associated with an 8-day earlier delivery

ERGO

Preston and Fruh et al, Environ Res, 2021

Association between Hair Product Use and Birth Weight



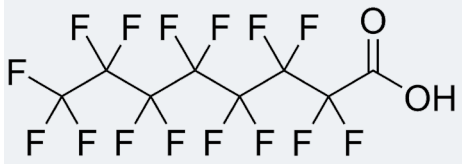
Use of hair oils was associated with a 300-gram lower birth weight

Chan et al, Env Res 2023

Two examples:

1. Phthalates and cardiovascular disease risk
2. **PFAS and cardiovascular disease risk**

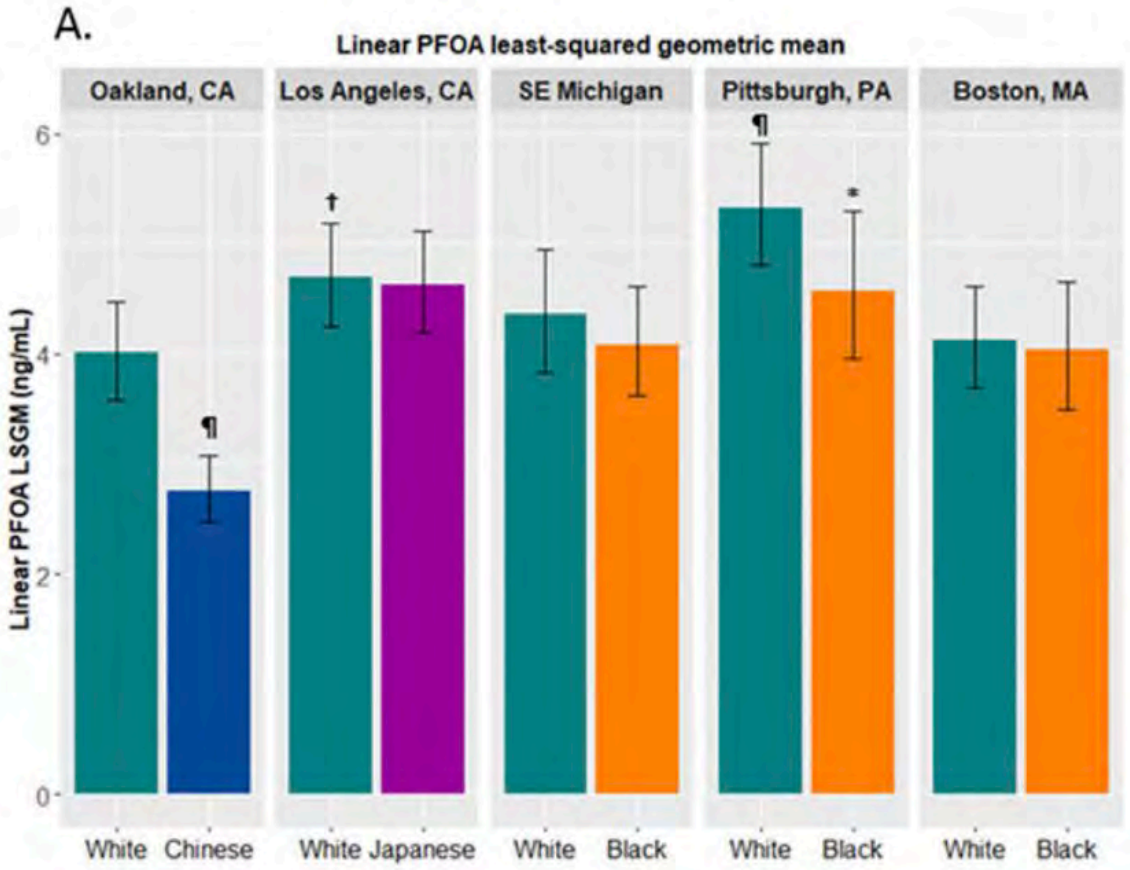
Examples of disparities in environmental chemical exposures

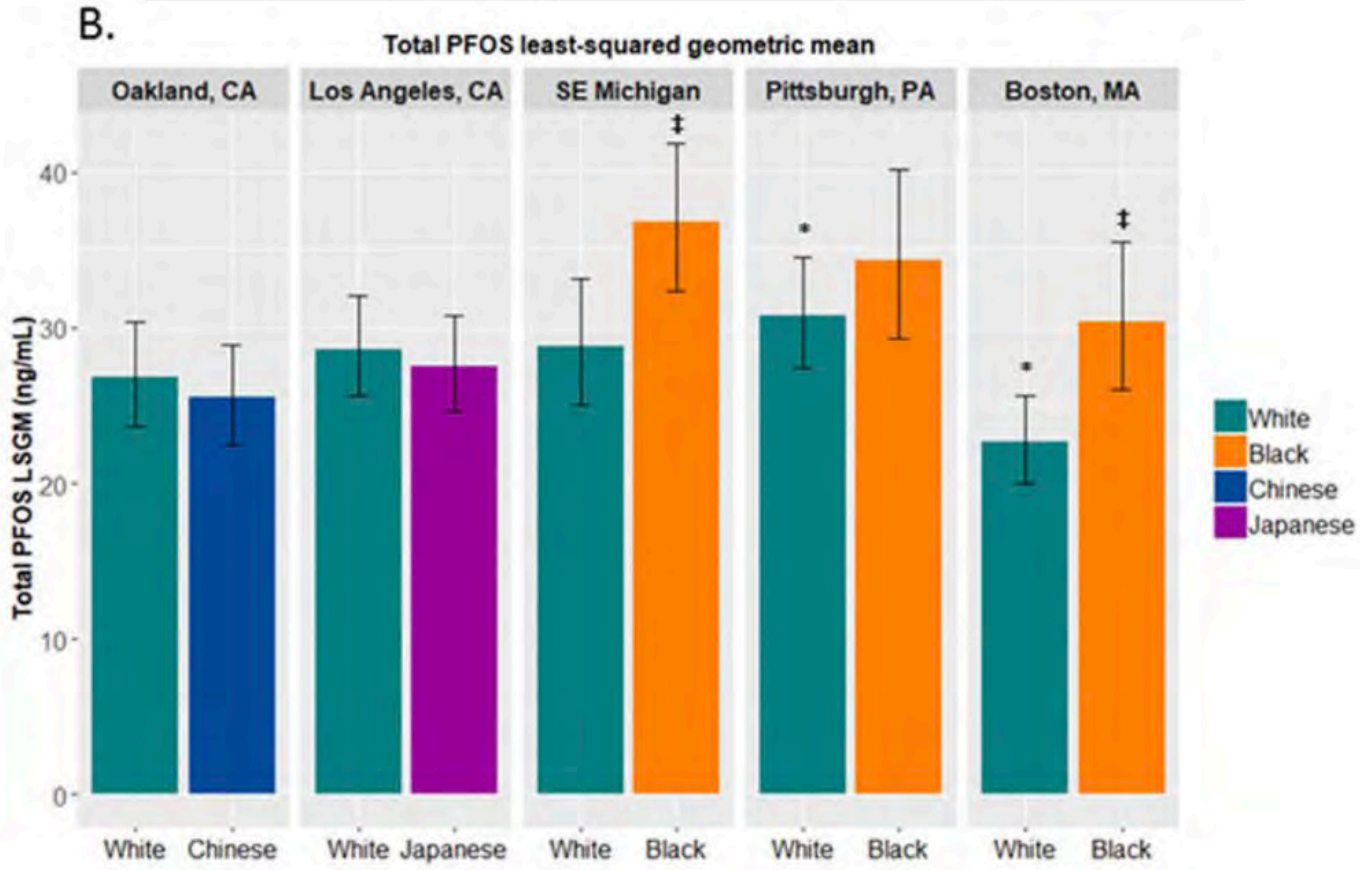


PFAS

Examples:

- ❖ Contaminated water
- ❖ Consumer products
- ❖ Occupational exposure





Park et al, Env Res, 2019

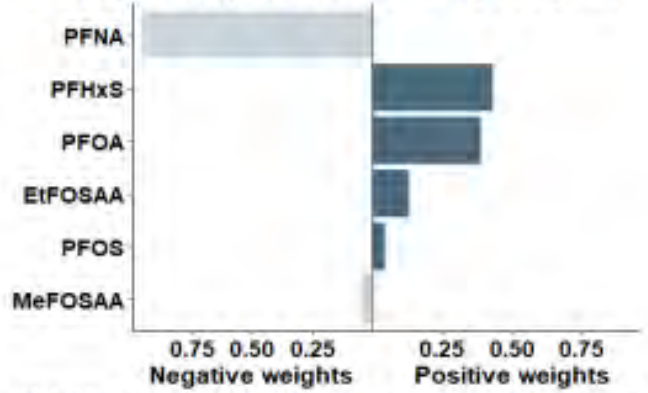
PFAS mixtures and hypertensive disorders of pregnancy

PFAS Mixture

Quantile g-computation results: effect of the PFAS mixture on the odds of GH & PE

- Each quartile increase in the PFAS mixture was associated with **1.40 (95% CI: 1.04, 1.87) greater odds of GH vs. Norm**

Figure 2. Quantile g-computation estimated PFAS weights for GH vs. Norm



Weights correspond to the proportion of the overall mixture effect in either the (+) or (-) direction for each individual PFAS

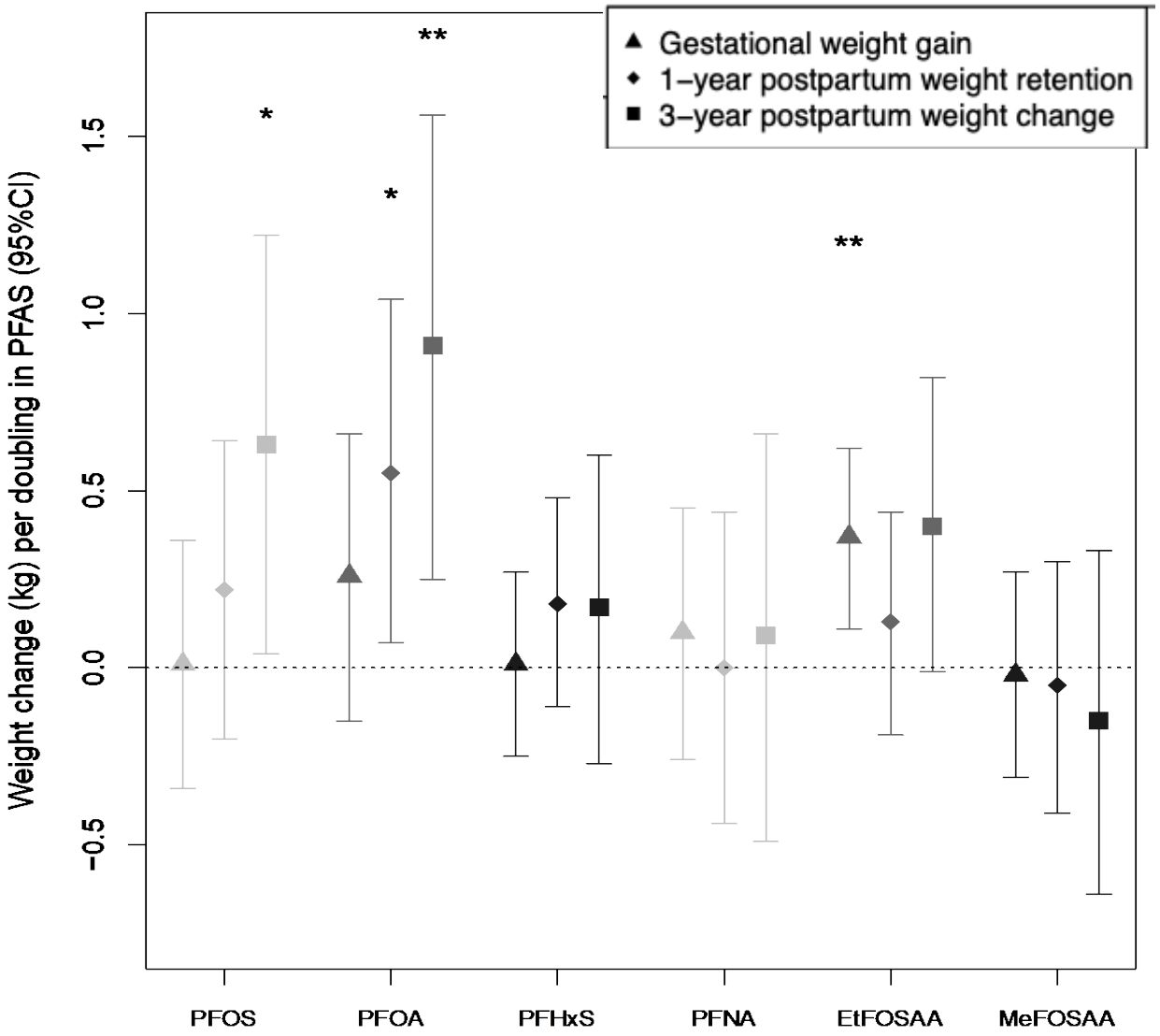
- The PFAS mixture was not associated with PE

- PFAS mixtures are associated with 40% increased odds of gestational hypertension
- PFHxS, PFOA, EtFOSAA, and PFOS contribute positively to the association between PFAS mixture and gestational hypertension
- No association between PFAS mixture and preeclampsia

All estimates adjusted for age, marital status, race/ethnicity, education, smoking

Preston et al, Env Int 2022

PFAS and Maternal Weight from Pregnancy to 3 years Postpartum



- Women gained 0.37 kg (95% CI: 0.11, 0.62) more **gestational weight** per doubling of EtFOSAA
- Women retained 0.55 kg (95% CI: 0.07, 1.04) more **at 1-year postpartum** per doubling of PFOA
- **3-year postpartum** : women gained
  - 0.63 kg (95% CI: 0.04, 1.22) more per doubling in PFOS,
  - 0.91 kg (95% CI: 0.25, 1.56) more per doubling in PFOA, and
  - 0.40 kg (95% CI: -0.01, 0.82) more per doubling in EtFOSAA

All estimates adjusted for age, pre-pregnancy BMI, marital status, race/ethnicity, education, household income, smoking, and parity

Mitro et al, Obesity 2019

From Documenting to Doing—Action Steps for Environmental Justice Epidemiologic Research

Identified a potentially modifiable risk factor!

Race/ ethnicity → *Environmental racism*
- *Structural/ place-based factors*
- *Cultural/ Behavioral*
- *Accessibility*
- *Availability*

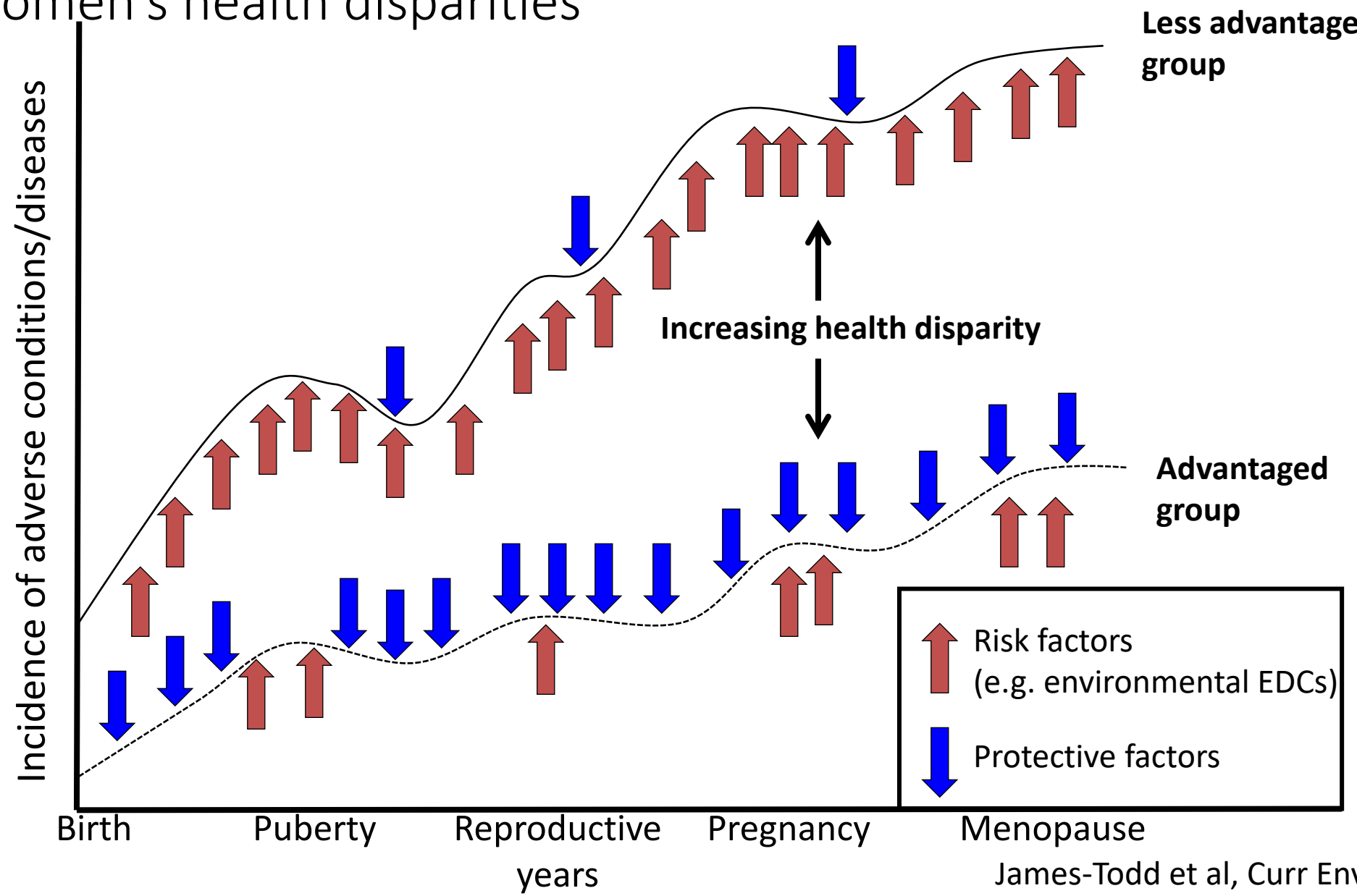
→ *Endocrine disrupting chemicals* →
- *Preterm birth*
- *Low birth weight*
- *Postpartum weight retention*

→ *CVD risk*

Considerations for improving research methods for addressing EDC-associated health disparities

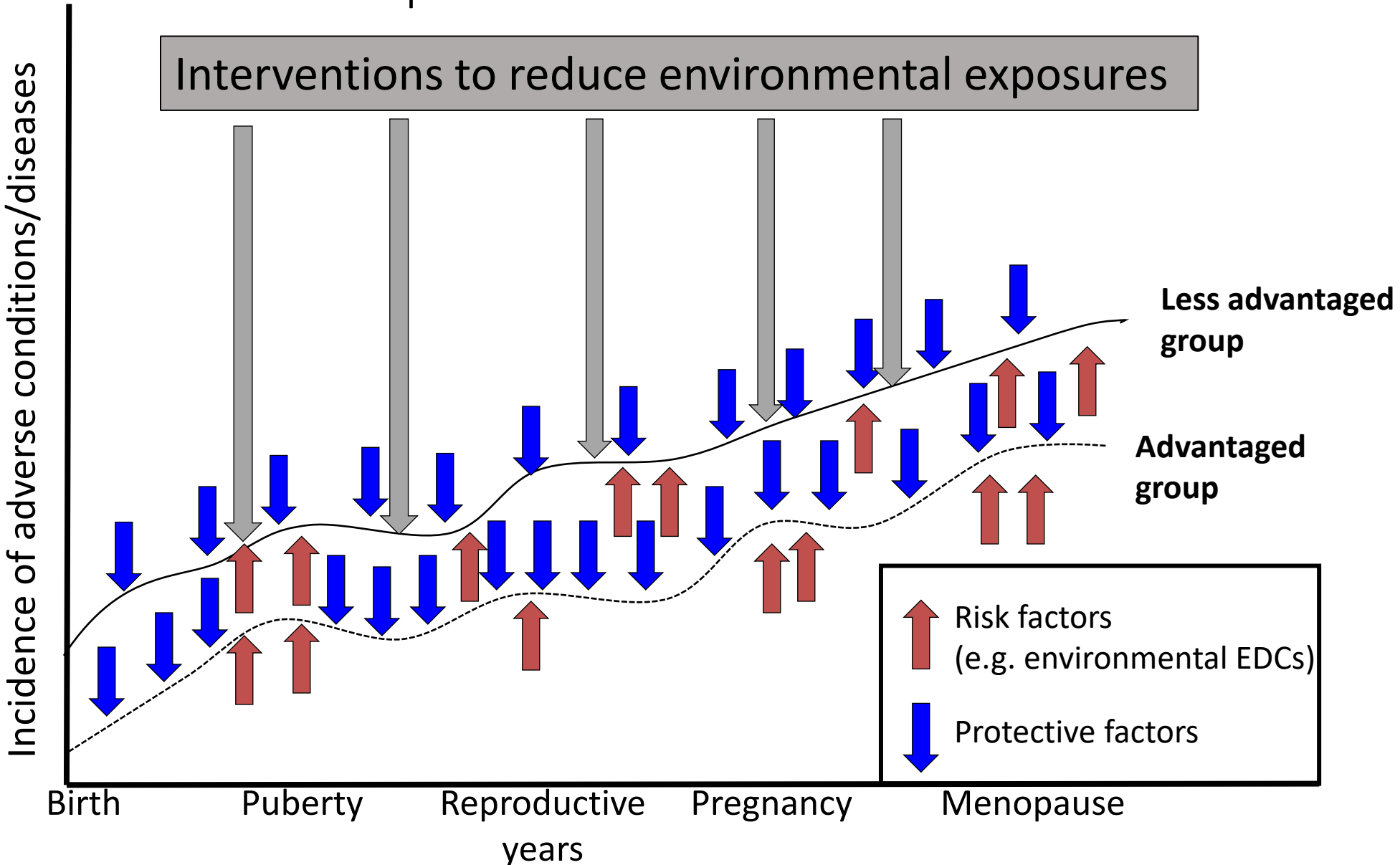
- Improve exposure assessment
- Expand toolkit of statistical methods
- Include mixed methods research – qualitative methods are equally important
- When enough information is available, consider intervention development
- Implementation science and effectiveness research
- Partner with communities and investigators in other fields

Contribution of unequal environmental exposures to increasing risk of adverse women's health disparities



James-Todd et al, Curr Env Hlth Rep 2016

Contribution of unequal environmental exposures to increasing risk of adverse women's health disparities



Acknowledgements

Environmental Reproductive Justice Lab: Marlee Quinn, MPH; Emma Preston, PhD; Kathryn Tomsho, PhD; Zifan Wang, MS; Marissa Chan, MS; Jordan Arvayo, MS; Azariah Boyd, BA; Gerardo Rodriguez, BA

ERGO/LIFECODES Study Team: Michele Hacker, ScD, Blair Wylie, MD; Thomas McElrath, MD, PhD; Ellen Seely, MD; Florence Brown, MD; Russ Hauser, MD, ScD; Paige Williams, PhD; Andrea Bellavia, PhD; David Cantonwine, PhD; Camille Powe, MD; Shruthi Mahalingaiah, MD; Karen O'Brien, MD; Marlee Quinn, MPH; Zifan Wang, MS; Emma Preston, PhD; Victoria Fruh, PhD, Antonia Calafat, PhD; Xiaoyun (Sherry) Ye, MS

Review article and conceptual model: Andrea Bellavia, PhD; Yu-Han Chiu, MD, ScD; Linda Valeri, PhD; Ami Zota, ScD

NHANES Study: Tianyi Huang, ScD; Richard Stahlhut, MD; Russ Hauser, MD, PhD; Sheena-Gail Powell, BS; Janet Rich-Edwards, ScD, Susanna Mitro, PhD; MyDzung Chu, PhD; Robin Dodson, ScD; Gary Adamkiewicz, PhD; Lucy Chie, MD; Florence Brown, MD

Project Viva PFAS: Emma Preston, PhD; Marie-France Hivert, MD; Abby Fleisch, MD; Sharon Sagiv, PhD; Wei Perng, PhD; Sheryl Rifas-Shiman, MS; Jorge Chavarro, MD, PhD; Emily Oken, MD; Ami Zota, ScD; Susanna Mitro, PhD

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Questions?

Contact: tjtodd@hsph.harvard.edu

For more information, visit the
Environmental Reproductive Justice Lab at:
https://projects.iq.harvard.edu/james-toddlab

Advancing Health Equity

Tonya Sharmaine Lane, M.S.

Cosmetic Chemist

Curly Chemistry

VIDEO RECORDING


Break
We will resume in Gather.Town at 11:15AM

Virtual Poster Session

Gather.Town

11:15AM – 12:30PM

Join us in Gather.Town for the Virtual Poster Session

How to Join Gather.Town

- Please join our sessions **currently in progress** in Gather.Town
- **The Gather.Town link is available in the chat box as well as on the website.**
- Detailed Gather.Town instructions can also be found on the website.
- Abstracts and posters are viewable on the symposium website and in Gather.Town.
- For assistance, please send a direct message or email to the contracting team:
  - Damon (RLA), damon.kane@roseliassociates.com
  - Sofia (RLA), sofia.jones@roseliassociates.com

Symposium Website

Upcoming Agenda

11:15 – 12:30 PM Virtual Poster Session in Gather.Town

12:30 – 1:00 PM Lunch


Lunch
We will resume at 1PM

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Alexandra Destler

SafetyNEST

Robin Dodson

Silent Spring Institute

Emily Hilz

Individual

Tiffany St. Bernard, Ph.D.

My Hair Days

Dr. Greg Hall, M.D.

National Institute for African American Health (NIAAH)

Erin Speiser

Hackensack University Medical Center

Jacqueline Brown

Empowerment Resource Center, Inc.

Moderated by Margaret Snyder

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Alexandra Destler

SafetyNEST

SafetyNEST®

Alexandra Destler, Founder & CEO: Alexandra@mysafetynest.com

WOMEN OWNED

Mission

Our mission is to dramatically reduce the incidence of preventable diseases linked to toxic chemicals and safeguard the future generations so they can grow and thrive.

AGENDA

- Why I Started SafetyNEST
- What I've Learned
- How We're Reaching Women to Safeguard Future Generations

Daily Exposure to Dangerous Toxic Chemicals

85,000 chemicals surround us daily
from flame retardants in bed mattresses to lead in lipstick.

Less than 1% of these chemicals
are tested by the EPA for safety or toxicity.

No enforcement in the US
that new chemicals be tested for safety
before chemicals go to market.

Early Exposure to Toxics is Directly Linked to Diseases

Early life toxic exposures can have **harmful effects across the full life span.**

Since the 70s…

- Rates of **childhood cancers are up 40%**
- **Learning disabilities now affect 1 out of 6 children** born in the US
- **Childhood asthma & obesity have tripled.**

Diseases linked to toxic chemicals:

- **Preterm birth**
- **Birth defects**
- **Diabetes**
- **Obesity**
- **Asthma**
- **Childhood cancers**
- **ADHD and other behavioral and cognitive problems.**

Childhood obesity has more than **doubled in last 30 years.**

***Sources**: UCSF Program on Reproductive Health and the Environment Icahn School of Medicine at Mount Sinai, Children's Environmental Health Center.*

Existing Health Care Gap
Safeguarding the Next Generation

Moms-to-be and New Families

are **unaware of risks or frustrated** & **lack credible guidance** on what's safe and what's not safe in their home.

Reproductive Health Professionals

Lack training, tools and expertise to counsel patients when women are motivated to make behavior change.

UCSF Health: https://obgyn.ucsf.edu/news/fewobcounseltoxins

All Women Want a Trusted, Easy & Reliable Solution.

What We Learned

Top Changes for a Healthier Pregnancy and Baby

How We're Reaching Women

Trusted Content

BetterNest ™ Score

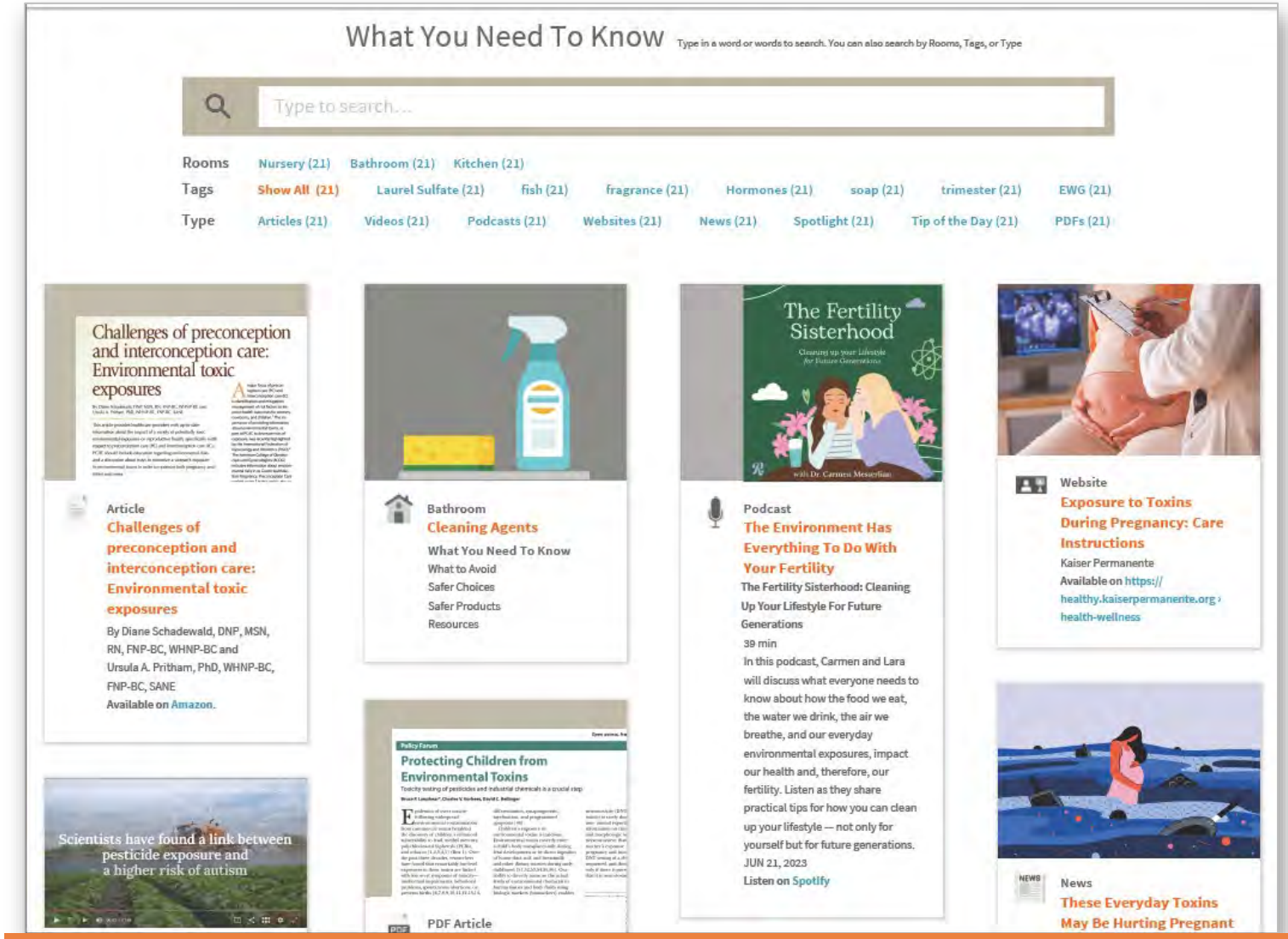
Health Professional Resources

Wellness Market

Social Media

Be the Change!

Trusted Content



CDC
Centers for Disease Control and Prevention

PEHSU
Pediatric Environmental Health Specialty Units

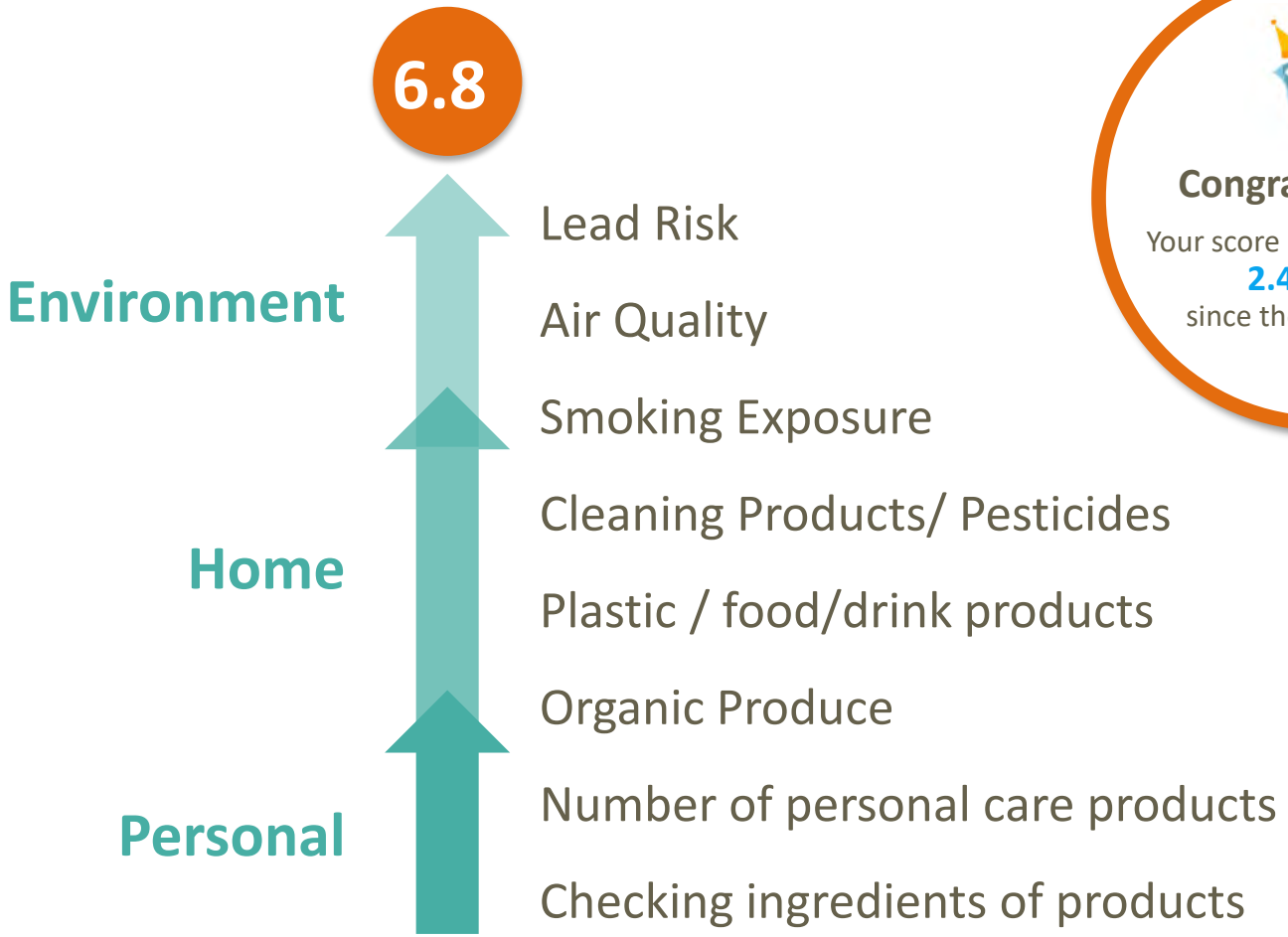
NIH
National Institute of Environmental Health Sciences

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

EPA

Accurate, Actionable and Affordable Guidance

BetterNest™ Score



Congratulations!

Your score has increased by
2.4 points
since the last update.

Accurate, Actionable and Affordable Guidance

Wellness Market

Your Location

95549

Desired Distance

Within 25 miles

Select a Category

- Fertility
- Lactation
- Doulas and Midwives
- Mental Health
- Acupuncture
- Home Green Audit

Tender Gifts Midwifery & Birth Center

Midwifery Circle City Women's Health Services Inc

East County Midwives

Fruitful Vine Midwives

Birth in Color Midwifery, LLC

Artemis

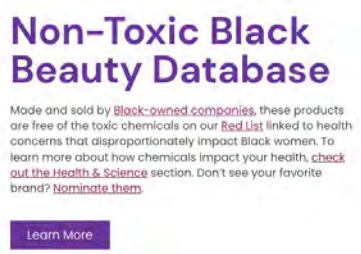
SafetyNEST on Social

YouTube

TikTok

Accurate, Actionable and Affordable Guidance

Safer Products – How to Find



Be the Change!

Engage in action to drive change locally and domestically by advocating for fair environmental health JUSTICE and protection policies.

SafetyNEST®

Re-Launching Fall 2023:
www.mysafetynest.com

Contact:
Alexandra@mysafetynest.com

Thank you.

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Robin Dodson
Silent Spring Institute

Product Options in Women-Engaged Research (POWER) Project

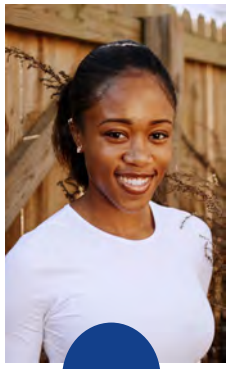
Dr. Elissia Franklin, Aleyana Momplaisir, Lilly Marcelin, Dr. Robin Dodson

SILENT SPRING INSTITUTE
Researching the Environment and Women's Health

Resilient Sisterhood Project
A Window into Women's Reproductive Health and Wellness

Silent Spring Institute

Silent Spring Institute is a leading scientific research organization dedicated to understanding the links between environmental chemicals and women's health.



SILENT SPRING INSTITUTE
Researching the Environment and Women's Health

Resilient Sisterhood Project

RSP is a non-profit organization raising awareness and empowering women and young adults of African descent affected by diseases of the reproductive system.

Resilient Sisterhood Project
A Window into Women's Reproductive Health and Wellness

Putting together a team for social media influence

1. Identified 50 social media content creators across multiple niches
2. Pitched over 30 creators to be a part of the POWER team
3. Onboarded a team of 10 social media influencers

Influencer Deliverables

- Attend interactive and informational workshop
- Create and post 1-2 content pieces for social media
- Share a survey with their audience
- Report post analytics and audience feedback

SILENT SPRING INSTITUTE
Researching the Environment and Women's Health

Resilient Sisterhood Project
A Window into Women's Reproductive Health and Wellness

Instagram Post

Metrics

25,000+
Views

1800+
Likes

80+
Saves

60+
Shares

A wide range of content is being created

N'Dea

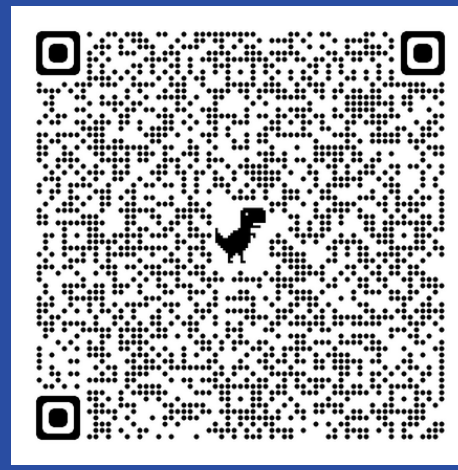
@bmekween

TikTok

Beverly

@curlybeviie

Instagram



Korie

@teamkorie

LinkedIn

Robyn

@robynmneal

Instagram Reel

Audience feedback

74%

Increased their concern about how chemicals in products may affect their health

83%

Previously heard about chemicals in products affecting health

43%

May start avoiding chemicals of health concern in the products that they purchase

Based on 187 survey participants

> So true and very personal for me since I have also had similar struggles! Thanks for sharing and working towards educating more black women about how we can take more informed care of our bodies. 🙌♡

> Thanks, [...] for this Call to Action! [...] This beautiful reminder recharges us to take ownership.

> I really love this! I'm really critical about what I put in and put on my body but I still have so much to learn about the different chemicals that go into these everyday products..

From LinkedIn and Instagram viewer comments

Our impact

Metrics

114,000+

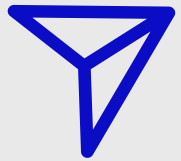
Views

8700+

Likes

900+

Saves



1400+

Shares

Is social media an effective way to reach Black women with information about EDCs in products?

Connect with us

SILENT SPRING INSTITUTE
Researching the Environment and Women's Health

www.silentspring.org
@SilentSpringIns
@silentspringinstitute
@silentspringinsitute

Resilient Sisterhood Project
A Window into Women's Reproductive Health and Wellness

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Pole fitness | Liberation

Robyn

@robynmneal

Food | Lifestyle

Lisa

@fitlisag

Fitness | Health

Korie

@teamkorie

Science | Lifestyle

Camille

@iamcamillesmith

Beauty | STEM

Beverly

@curlybeviie

Beauty | Lifestyle

N'Dea

@bmekween

Sustainability | Lifestyle

Ijeoma

@ijeomakola

Lifestyle | Empowerment

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

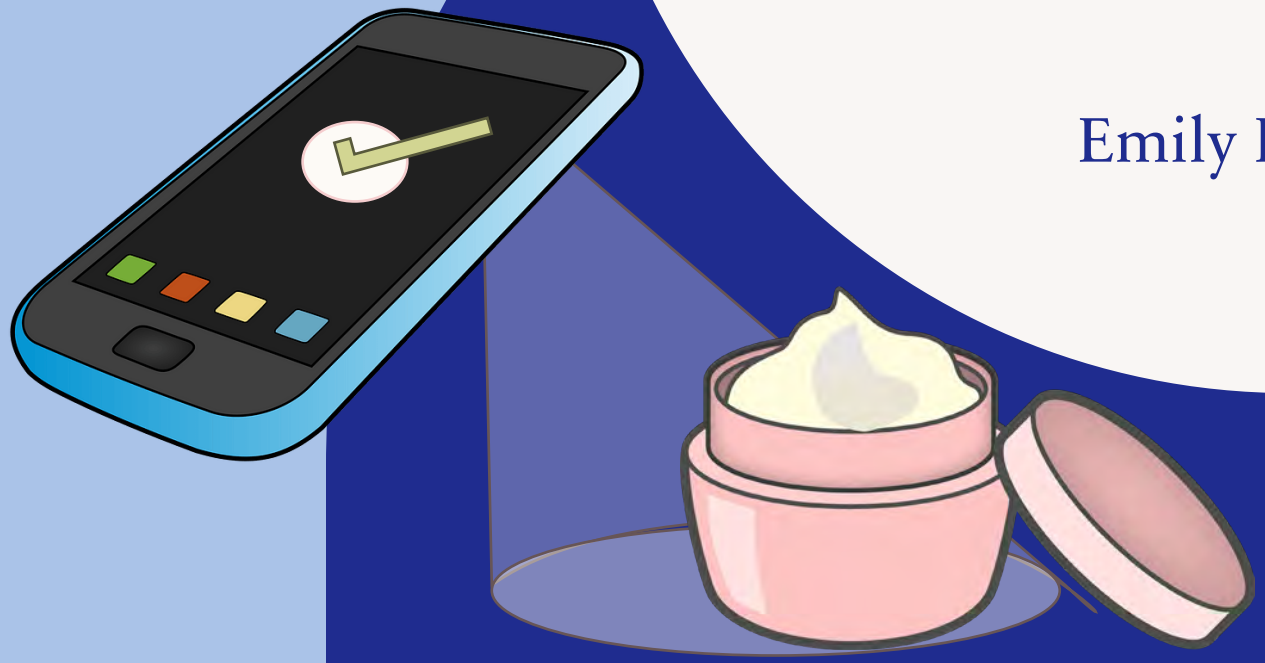
Emily Hilz

Individual

ENDOSCREEN:

AN APP FOR INCREASING BLACK WOMEN'S AWARENESS OF EDCS IN PERSONAL CARE PRODUCTS

Emily Hilz, PhD



Public perception of the risk associated with the use of EDC-containing products is low.

- low awareness of personal routes of exposure such as in consumer products.

BLACK WOMEN ARE DISPARATELY EXPOSED TO EDCS VIA TARGETED CARE PRODUCTS

Black women are exposed to EDCs because of socioenvironmental factors:

- natural hair discrimination
- colorism
- stigma surrounding feminine hygiene

Modest reductions in exposure meaningfully improve health.

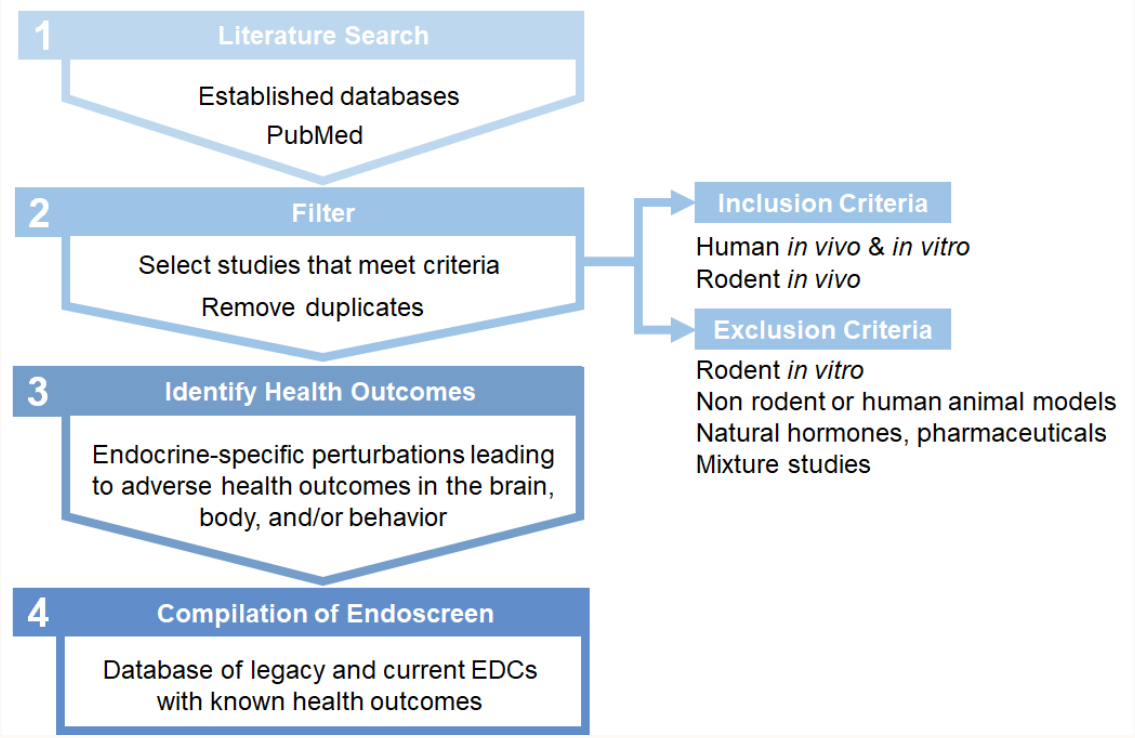
Dodson et al., 2021; James-Todd et al., 2012;
Bethea et al., 2020; Branch et al., 2015; Welch et al., 2022

ENDOSCREEN

Mobile app development to
increase awareness of / reduce exposure to EDCs

EDC DATABASE	OCR	REPORT BACK	OUTREACH	USER FEEDBACK
Built on a database of known and/or suspected EDCs + their adverse health effects.	Scans product ingredients list to recognize EDCs.	Reports information regarding detected EDCs and their associated health outcomes.	Designed with education in mind. Partner with black brand ambassadors, business owners, and community leaders.	Collection of non-identifying demographic information; patterns-of-use, demographics, and report back data.

THE DATABASE



Used systematic review to identify EDCs with known health impacts.

- Mix of automated (PubMed api) and manual scanning (specific chemical and outcome).
- Used frequency analysis to assess relevance.

Modeled after DEDuCT; updated methods and criteria, removed duplicates.

- Added ~1300 papers not included in DEDuCT 2.0 for a total of ~14,000 entries and 861 unique EDCs.

Karthikeyan et al., 2019, 2022

USER EXPERIENCE

SCAN A LABEL

"Optical Character Recognition" converts text from a picture to machine-readable format.

- Singles out letters and categorizes those as words that can be referenced to the database.

REPORT BACK

Provides a report to users about EDCs in their product(s)

- Health outcomes
- Number of peer-reviewed articles

Report back increases understanding and feelings of empowerment.

EDUCATION

Educational features include:

- What are EDCs?
- Health Impacts.
- Tips for avoiding EDCs.

Later releases:

- Personal exposure tracker.

(1) image acquisition (2) conversion to readable characters (3) Comparison to database & report back

REACHING THE BLACK COMMUNITY

"Endoscreen is designed to be used by any person in any circumstance… but we are working specifically to reach black women and members of their and other disproportionately exposed communities."

ENDOSCREEN IS UNIQUE

Works independently in real-time.
No manual databasing of individual products / backend screening staff.

EVIDENCE-BASED

Uses established accessible commination techniques.
Addresses uncertainty without undermining confidence.
Provides empowering action to choose between products.
Works to achieve these goals within a community context.

AND LIVE!

Visit **endoscreen.org** or scan the OR code to view our beta.
Our outreach campaign begins in earnest August 2023!

SCAN ME

ENDOSCREEN.ORG
Know what you're using

THANK YOU

HHS OFFICE ON WOMEN'S HEALTH

THE ENDOSCREEN TEAM:

EMILY HILZ
Project lead and research specialist

ROBERT PERCE
Full Stack Engineer;
SysAdmin & implementation

FORREST MCDONALD
Software engineer;
prototype & DB wrangling

ehilz@utexas.edu
emilyendocrine
Emily N. Hilz

SCAN ME

ENDOSCREEN.ORG
Know what you're using

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Tiffany St. Bernard, Ph.D.

My Hair Days

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Dr. Greg Hall

National Institute for African American Health (NIAAH)

NATIONAL INSTITUTE FOR AFRICAN AMERICAN HEALTH

& EDC Education

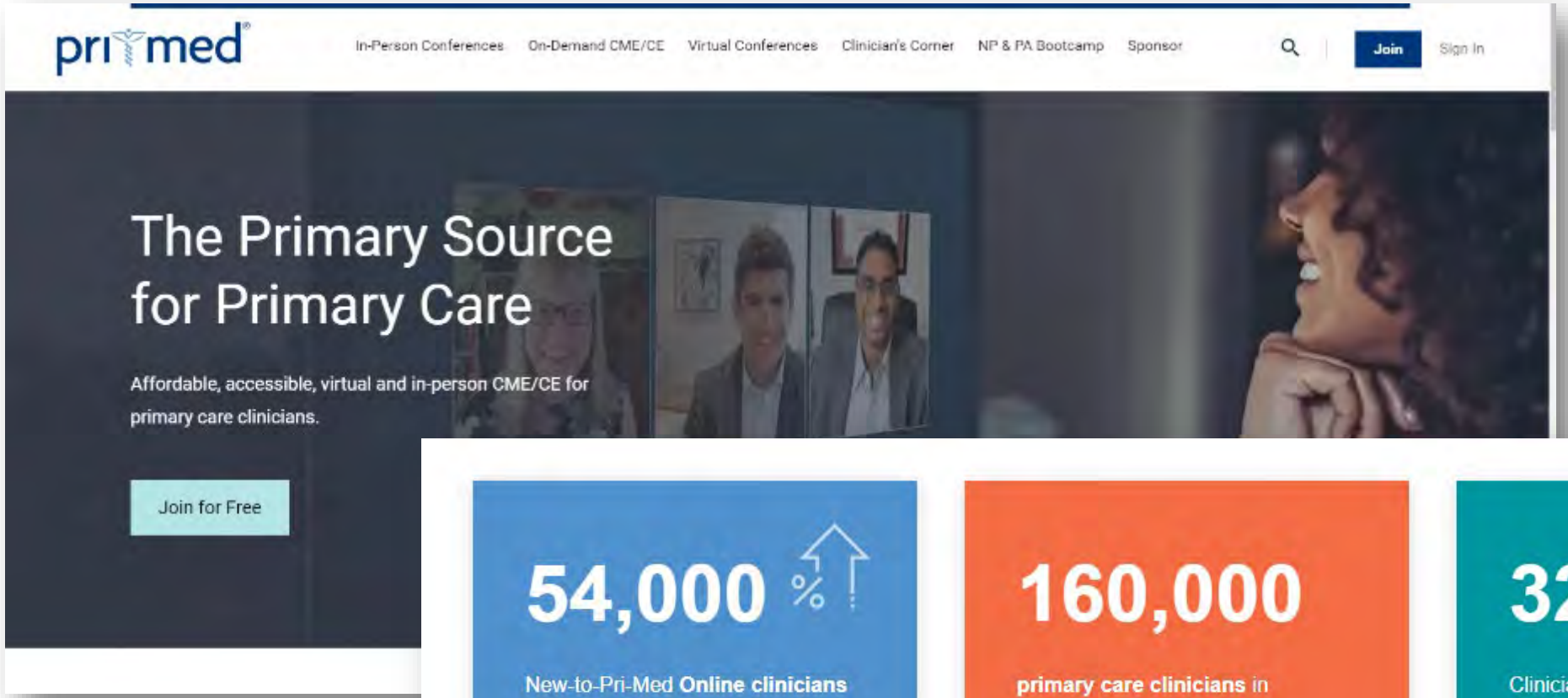
Gregory L. Hall, MD

Founder & Board Chair, National Institute for African American Health

Medical Director, Cutler Center for Men, University Hospitals of Cleveland
Associate Professor of Integrative Medical Sciences, Northeast Ohio Medical Univ.
Associate Professor of Internal Medicine, Northeast Ohio Medical Univ.
Assistant Clinical Professor in Medicine, Case Western Reserve University School of Medicine

Multipronged Approach to Education

- Physician Education
- On-line Resource
- Video Education with Social Media
- Podcast Interviews
- Community Partnerships



54,000

New-to-Pri-Med **Online clinicians** since 2020

160,000

primary care clinicians in Pri-Med's national database

32,590

Clinicians **registered** for *PrimaryCareNOW* in 2022

pri med

Bridging the Gap

Endocrine Disrupting Chemicals (EDCs) and their Impact on the Health of Women of Color

primed

Gregory L. Hall, MD

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Hormone Disrupting Chemicals (EDCs) are Throwing Black Women's Systems Off

by NIAAH Editors | Apr 23, 2023 | EDC & Black Women

By Essence Maston, PhD & Greg Hall, MDA lot has been written in the news about endocrine disrupting chemicals, or EDCs. Many of these chemicals are found in shampoo, lotions, conditioners, lipstick, makeup, moisturizers, sunscreens, creams,

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Is Plastic Damaging Black Women's Health?

by NIAAH Editors | Apr 23, 2023 | EDC & Black Women, Medical Experts & Research, Our Health | 0 comments

By Essence Maston, PhD & Greg Hall, MD

Many of the plastics that we use could be damaging to our health. Do you store food in plastic containers or even wrap food in plastic wraps? Science has shown that small amounts of dangerous chemicals are absorbed by the food while they are in direct contact. These chemicals could change the level of hormones in your body. Some believe the higher occurrence of infant and mother mortality, diabetes, and obesity may be related to these chemical exposures . . . particularly in African American women.

The overall safety of plastics has been the topic of many debates. Should plastic be banned? Should containers be re-used – if so, how many times is too many? What precautions should be taken? What is "BPA"?

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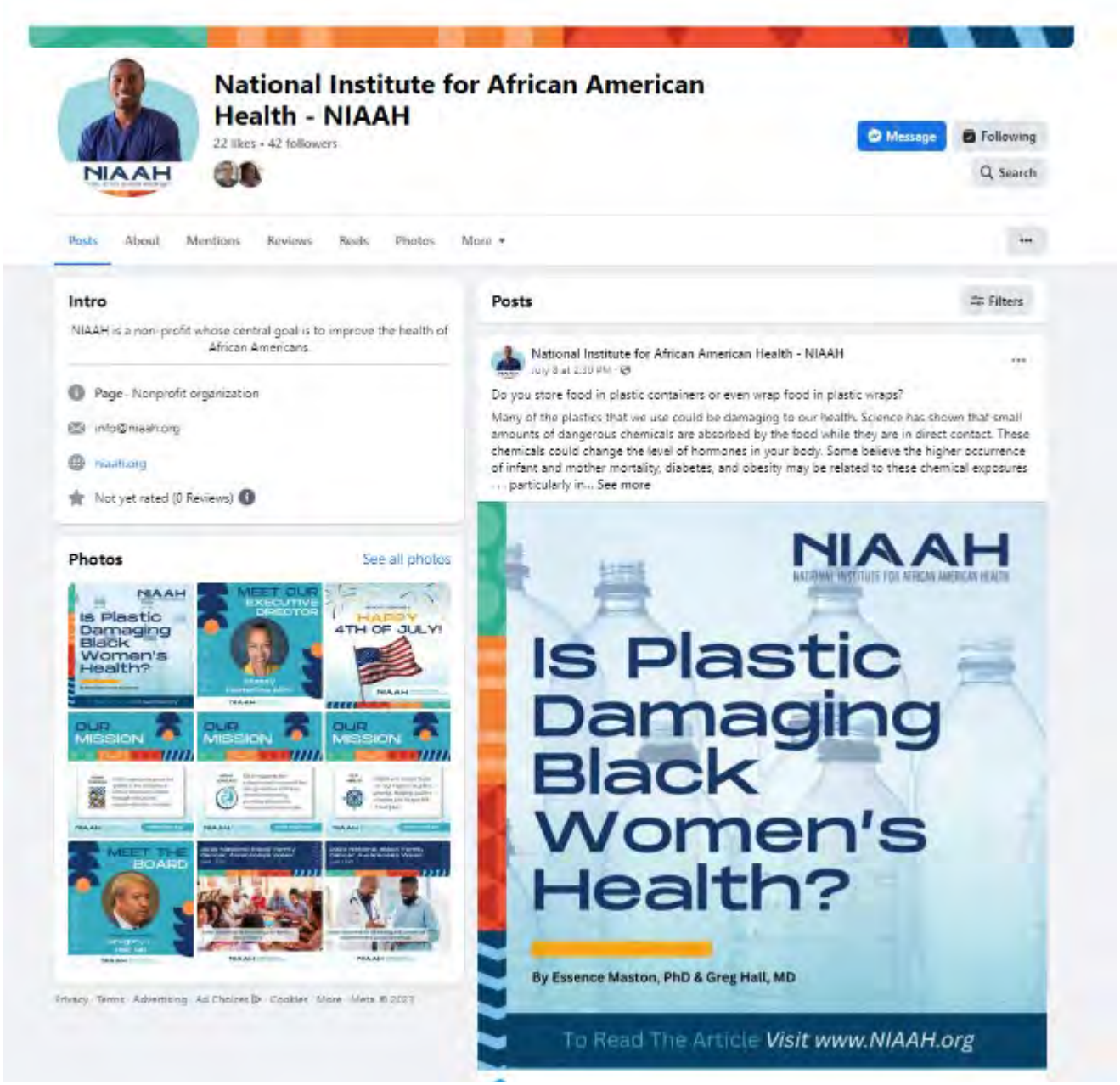


Instagram

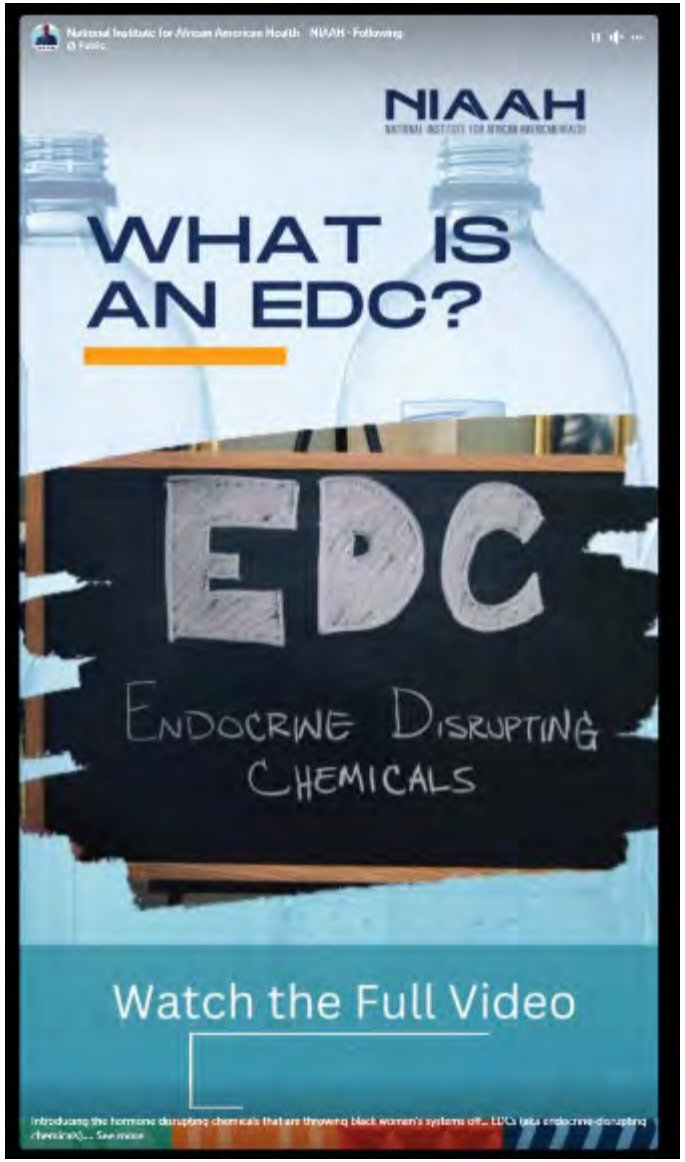

PLASTIC
VS
GLASS
BPA chemicals can leach into food and liquids
Non-toxic
May break down from overuse at high temperatures over time
Capable of withstanding high temperatures
Chemicals can change the level of hormones in your body (EDCs)
Free from EDCs
To Learn More: Visit www.NIAAH.org

Three Videos Produced for Our Campaign

Beyond the Surface: Examining EDC Exposure (FULL VIDEO)| EDC...

EDC Awareness "Two Women-Split Screen" Full Frame | NIAAH.org

"It's Just Hairspray" (Full Frame) | EDC Awareness Video | NIAAH.org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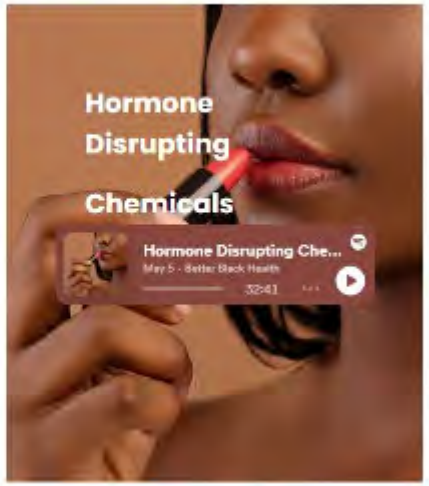
Get the latest health information and hear the most interesting people in the country talk about ways to improve your health



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The she Foundation, Incorporated

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Richmond Hts.
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NATIONAL CONGRESS OF BLACK WOMEN

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Beyond the Surface: Examining EDC Exposure (FULL VIDEO)| EDC...

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Supporting Health and Education Initiatives

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& EDC Education

primed

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Erin Speiser

Hackensack University Medical Center

New Jersey Healthy Salon Workers Training to Reduce Endocrine Disrupting Chemical Exposure Risk among Black Women

Reaching the next generation of cosmetologists

Erin Speiser, PhD, MA, CCRP – Principal Research Associate, Center for Cancer Health Equity, Cancer Institute of NJ, Rutgers University (previously at Hackensack Univ. Medical Center)

Traci N. Bethea, PhD, MPA – Assistant Professor, Office of Minority Health and Health Disparities Research, Georgetown Lombardi Comprehensive Cancer Center

Derek G. Shendell, D.Env, MPH – Professor, Department of Environmental & Occupational Health & Justice; Director, New Jersey Safe Schools Program (NJ SS), Rutgers School of Public Health

Background

- Hairdressers and stylists, barbers, nail technicians, aestheticians and other salon professionals work daily with a wide variety of chemicals, many of which have hazardous properties.

- Research to date has documented that chronic exposure to chemical toxicants currently found in hair and nail preparations can cause adverse health effects such as contact dermatitis, asthma and allergies, and may increase risk of cancer and negative reproductive outcomes.

https://thenounproject.com/

Background (cont.)

- Hair care and styling products are particularly important as they include chemical relaxers, bonding glues for hair extensions, and other products containing chemical mixtures - a potential “toxic soup” of ingredients not tested for long-term health and safety.

- To date, there is no known cosmetology training program for Black/African American (AA) salon workers including both content on the health hazards of endocrine disrupting chemicals (EDCs) and how to protect oneself from exposure in the salon setting.

Our HHS Challenge Study

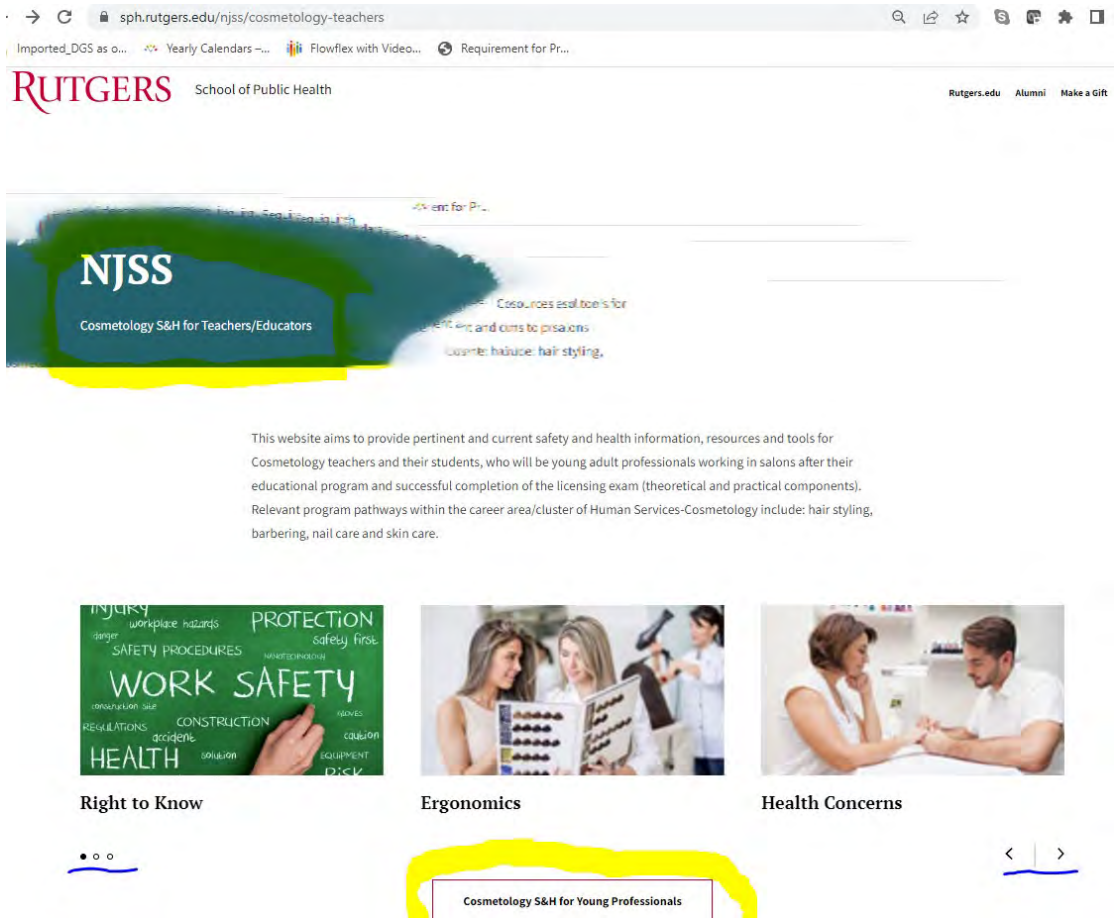
- To help protect the safety and health of these future cosmetology workers (and their clients), we created 2 educational modules on EDCs that have been added to and will be assessed as part of an existing training through the NJ Safe Schools Program from Rutgers School of Public Health:
  - Unit #1: Introduces the racial/ethnic disparities related to salon products and practices that lead to disproportionate EDC exposure among Black/AA women.
  - Unit #2: Focuses on steps that Black/AA students can take to protect themselves from EDCs at work (including alternatives to common EDCs containing products) and how to educate future owners/supervisors and clients.

NJ Safe Schools Program (NJSS)

https://sph.rutgers.edu/njss/home

NJSS home page links to:

- Cosmetology S&H for Teachers/ Educators
- Cosmetology S&H for Young Professionals



Launch of the Educational Intervention

- Our team developed content pages – information, photos and other visuals with sources, and links to websites or PDF files – that were integrated into the Rutgers Canvas Learning Management System, an asynchronous online learning platform

- Five teachers completed a preview pilot in Spring/Summer 2023:
  - 3 in Somerset County, NJ
  - 2 in Essex County, NJ

- The full rollout with students will occur in Fall 2023, followed by data analysis of the assessment measures

Lesson objectives (example from new modules)

View All Pages

Objectives Topic 4 Part II

Objectives for lesson 4 Part II

We spend up to 90% of time indoors, where the air is often 2-5 times more polluted than outdoors.[1]

In this presentation, you'll learn about:

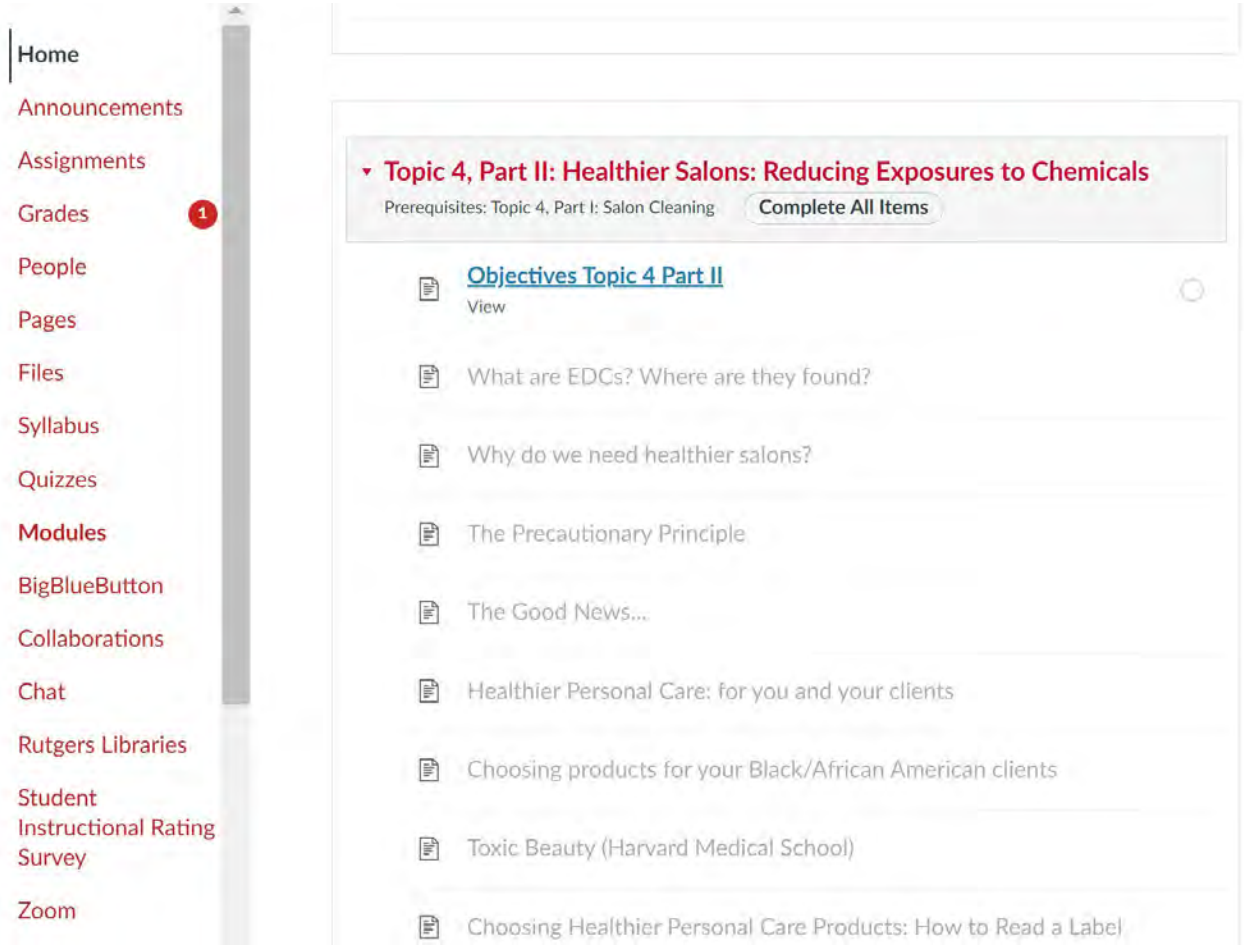
1. Identifying everyday exposures to chemicals in salons.
2. Simple changes can reduce exposures to positively impact salon worker safety and health and the health of clients.
3. Racial/ethnic disparities in salon products & practices.

References

1. US Environmental Protection Agency, Report on the Environment/Indoor Air Quality.

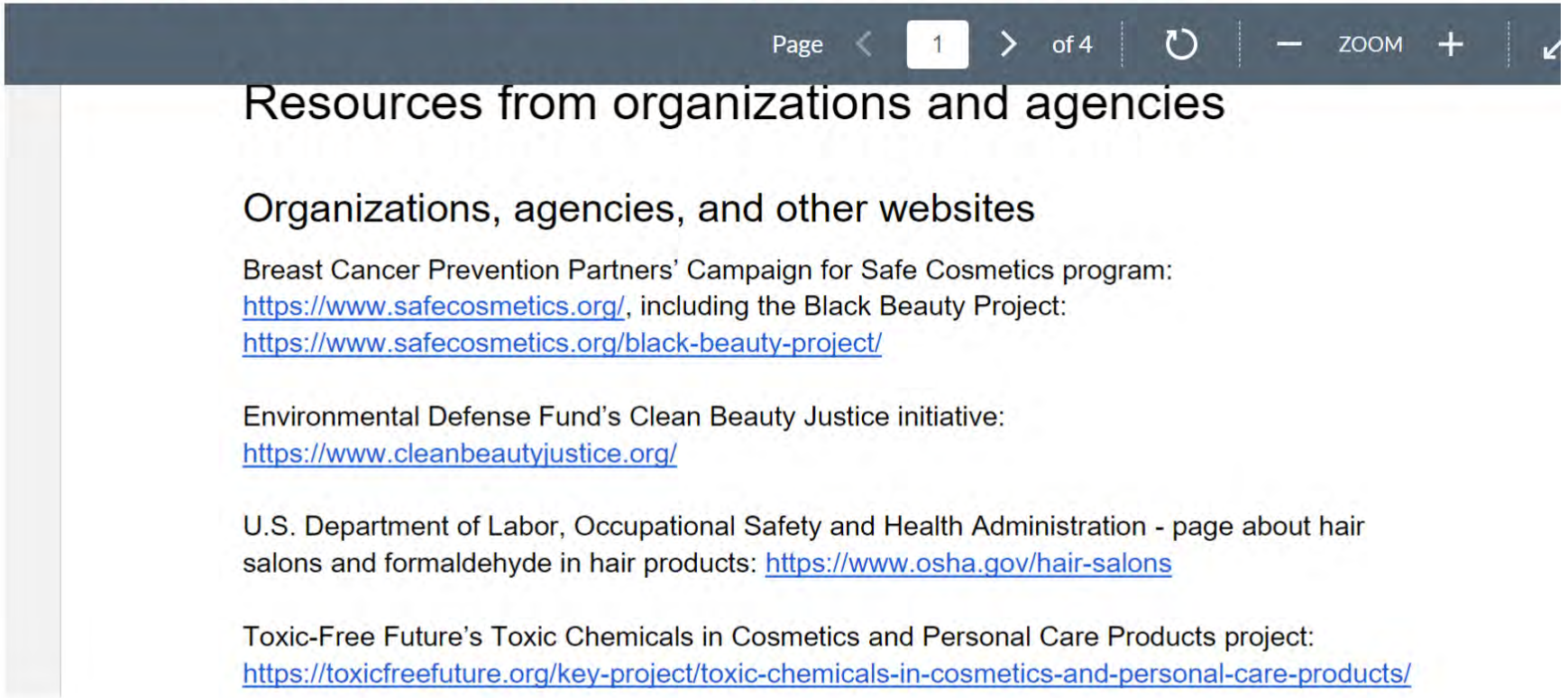
Previous

Organization of content in Canvas (partial list)



Additional resources for students (partial list)

Download Additional Resources for EDCs Module .pdf (108 KB) | Alternative formats



Case study for knowledge assessment (partial view)

View All Pages

Reducing Exposures to Chemicals Case Study

GiGi made an appointment at her neighborhood salon. She wanted the new keratin treatment for straightening hair that her best friend had tried.

GiGi had heard confusing news about this keratin treatment, including that someone said it used chemicals that could actually damage hair. Her mother said the chemicals could also harm her health.

Thank you!

Acknowledgements

- Midhat Rehman, MPH
- New Jersey Safe Schools Program, Rutgers School of Public Health
- HHS Office on Women's Health

HHS Endocrine-Disrupting Chemicals Innovator Award Competition Awardees

Jacqueline Brown

Empowerment Resource Center, Inc.

Endocrine Disrupting Chemicals & Women's Health Symposium

July 18th - 19th, 2023

Jacqueline Brown, MSPH MBA BS

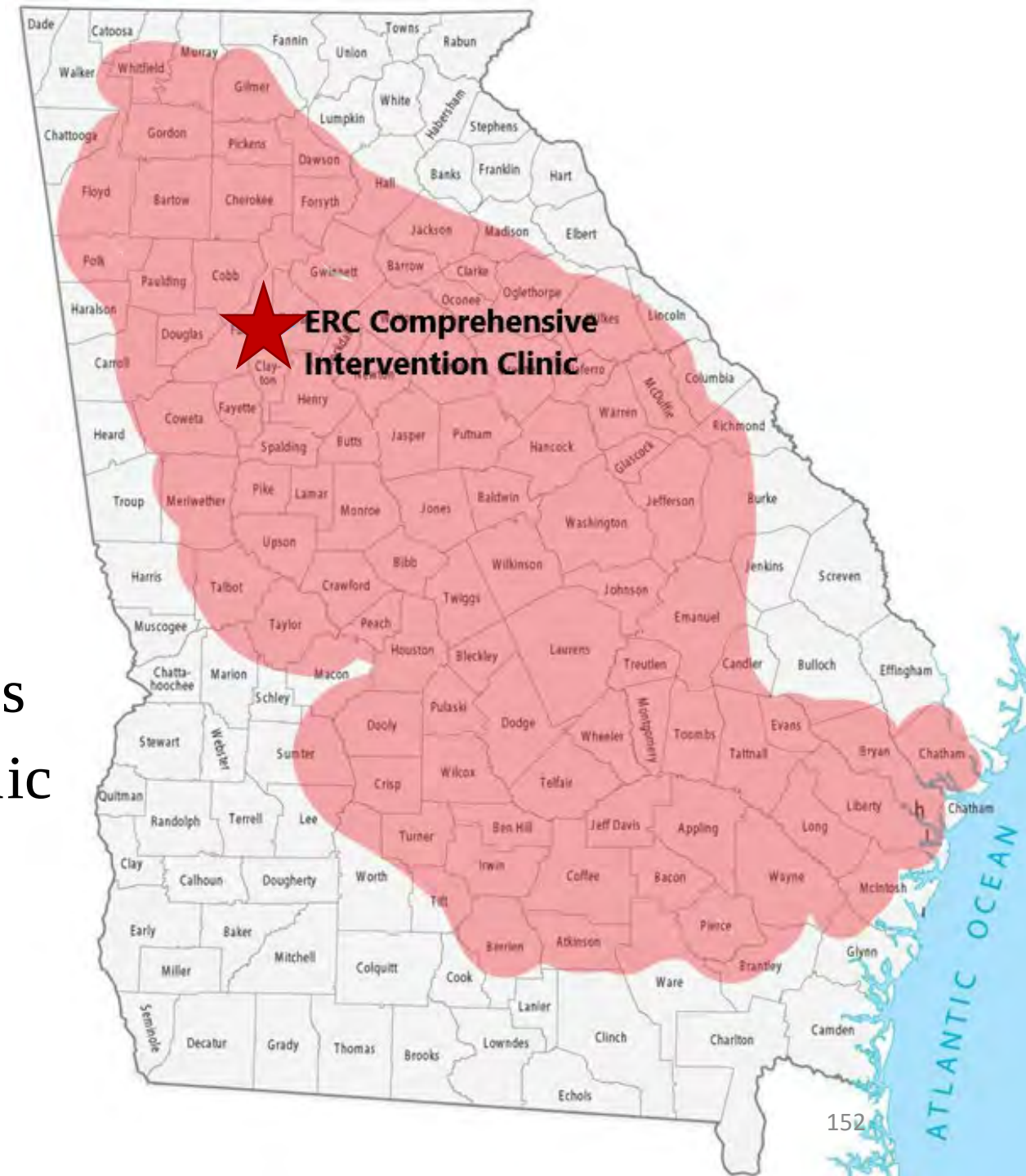
Chief Executive Officer

ERC Overview

- Established in 2003 and incorporated in 2006
- 20 Years of Operation
- A Non-Profit with 501(C)(3) Status
  - Community-Based Organization
  - Comprehensive Continuum of Care
- ERC Comprehensive Intervention Clinic
  - Georgia Composite Medical Board
  - Georgia Volunteer Health Care Program
  - Georgia DBHDD Provider and Community BH Clinic
- 3-Year Accreditation for Behavioral Health Services by CARF

ERC Overview

- Located in Atlanta, Georgia
- HHS HRSA 340B Covered Entity
  - STD
  - Ryan White
  - Family Planning Clinic
- Three HRSA 340B Eligible Facilities
  - Comprehensive Intervention Clinic
  - Clayton County BOH
  - ERC on the M.O.V.E.



ERC Overview

- Three Access Points for Services
  - Walk-in
  - ERC Telemedicine
  - Multiple Satellite Locations
- Multiple Contract Pharmacy
- Healthcare Accessibility
  - New to the Medicaid Arena
  - Accept Most Major Private Insurance
  - Sliding Fee Scale
  - Grant-Funded Services
  - Pursuing FQHC LAL Designation

Mission

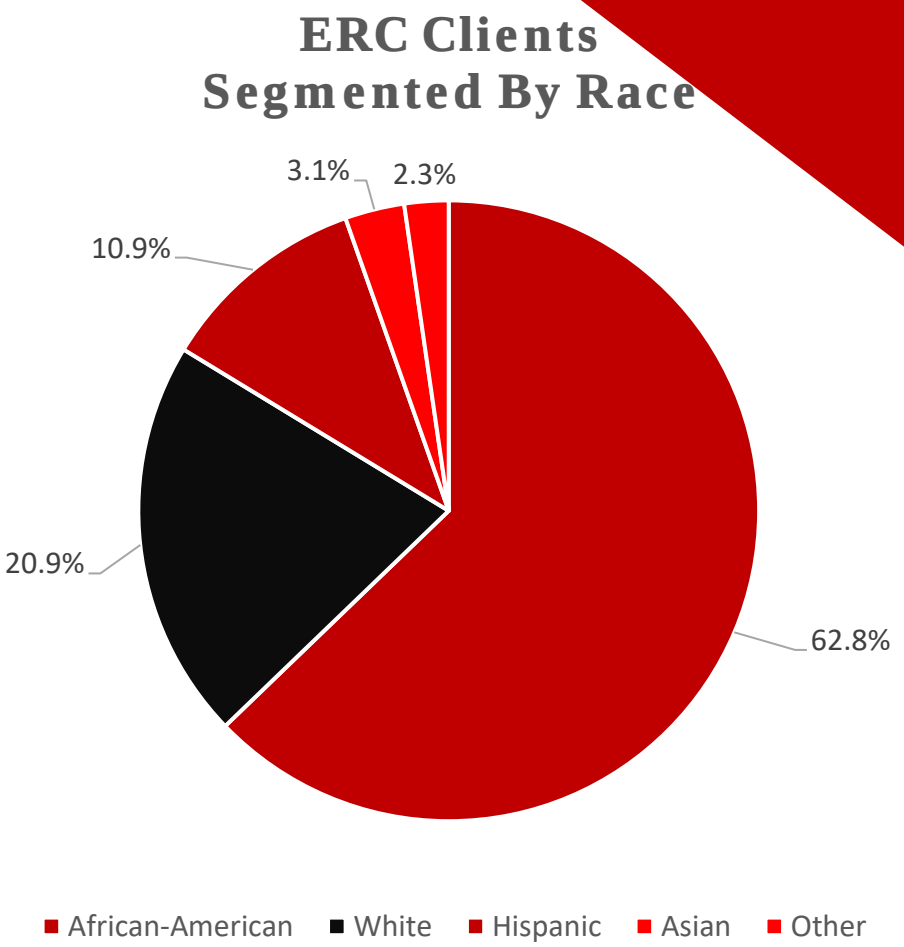
To Provide Programs, Services, and Community-level **Solutions** That **Improve** The **Health-related Quality of Life** for the Communities We Are **Privileged** to Serve.

Vision

Achieving Healthier Outcomes
One Client At A Time

ERC Client Pool Characteristics

- 39.0% Were Under the Age of 29
- 44% Uninsured
- 2.0% HIV Seropositive Rate
- 81.2% Linkage to Care Rate
- 15% Were Repeat Visitors for STI Services
- Gender Segmentation:
  - Male (66.0%)
  - Females (30.5%)
  - Gender non-conforming (2.0%)
  - Self-identified transgender (1.0%)



Endocrine Disrupting Chemicals

ERC Website Dedicated to Educate Black & African-American Women

- Inform on the Risk of EDC Use
- Educate about EDC Links to Cancers & Reproductive Health Issues
- List EDC Used in Household Products
- Share Strategies That Help to Reduce EDC Exposure

39% Likelihood of Black Women Dying from Breast Cancer Than White Women

Community Outreach Events

Additional Questions?

Jacqueline Brown, MSPH, MBA, BS
Chief Executive Officer
Empowerment Resource Center, Inc.
(404) 526-1145
www.ERC-Inc.org

Simple Ways Patients can Limit Exposure to EDCs

Leonardo Trasande, MPP, M.D.

Moderated by Margaret Snyder

Simple Ways Patients can Limit Exposures to EDCs

Leonardo Trasande, MPP, M.D.

Professor of Pediatrics

NYU Grossman School of Medicine

Break

We will resume at 2:45PM

Work Across the Government

Catherine Aubee, Sue Fenton, Tucker Patterson

Moderated by Margaret Snyder

Work Across the Government

Catherine Aubee

Senior Advisor for Endocrine Disruptor Screening Program

US Environmental Protection Agency, Office of Pesticide Programs

US EPA Endocrine Disruptor Screening Program

An Update for

HHS Office on Women's Health
Endocrine Disrupting Chemicals and Women's Health Symposium
Work Across the Government

July 19, 2023

Overview of U.S. EPA's Endocrine Disruptor Screening Program (EDSP)

Statutes & Organization

Congress passed the Food Quality Protection Act in 1996, which required EPA to screen pesticide chemicals for endocrine activity. In 2020, EDSP was integrated into the pesticide program.

Tiered Testing

EDSP uses a tiered approach to screen chemical. Tier 1 involves *in vitro* and *in vivo* screens for potential activity. Chemicals that move to Tier 2 are screened for adverse endocrine effects.

Chemical Lists

List of substances covered by the program and status on screening lists.

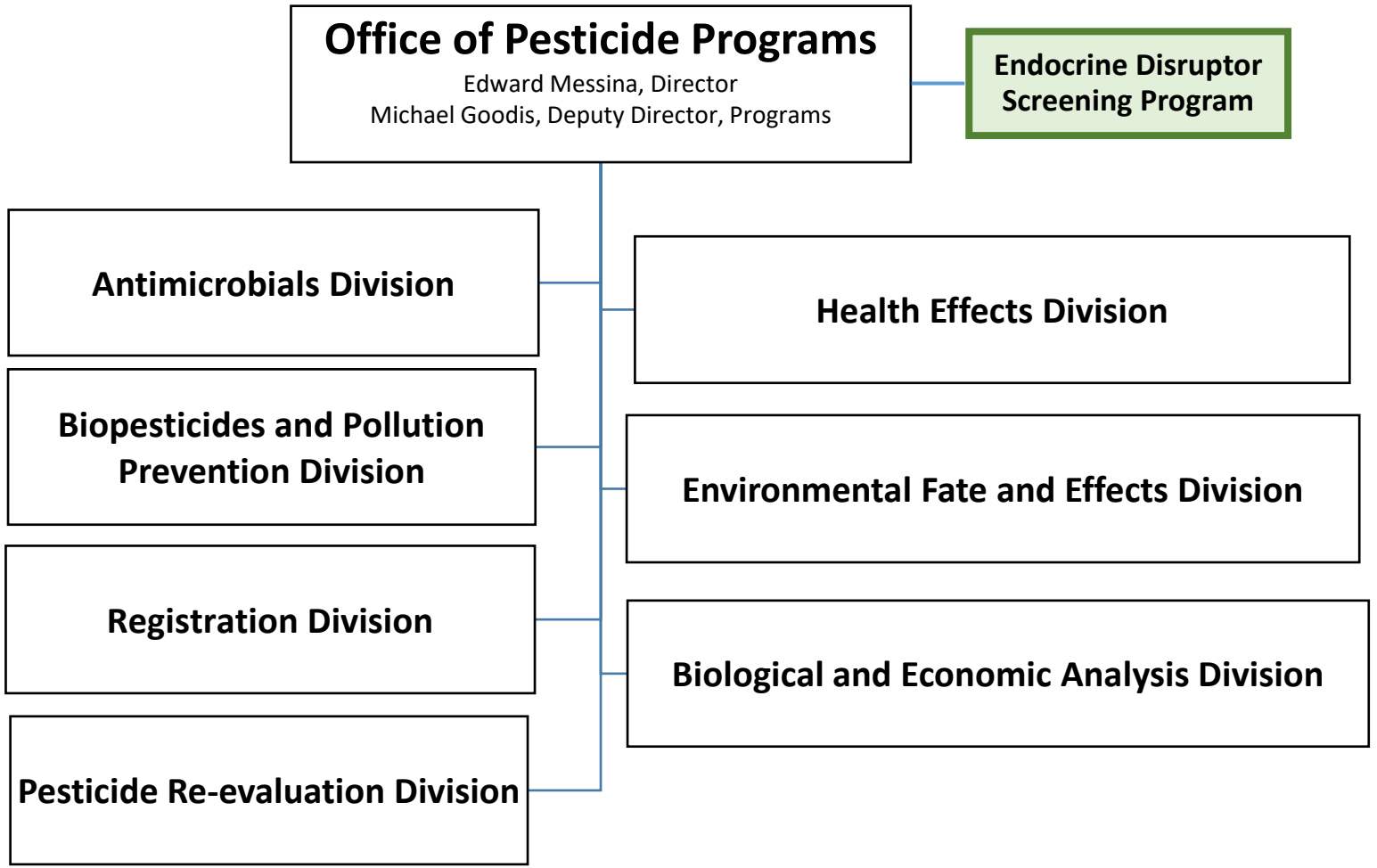
Alternative Methods

Cutting-edge technologies are used to prioritize chemicals and reduce, refine, or replace vertebrate animal testing. These are needed to increase the pace of chemical screening and testing.

Enhancing Efficiencies

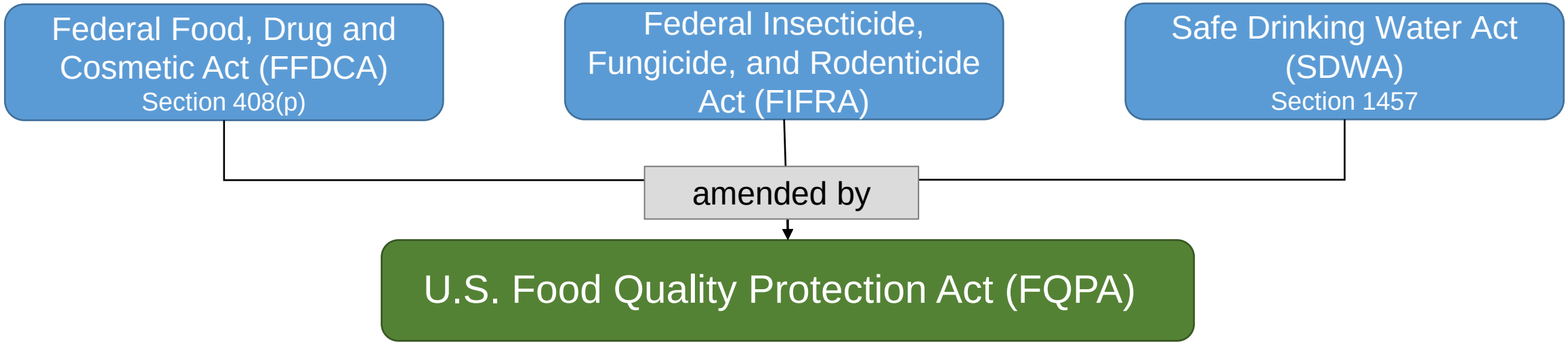
EDSP is enhancing efficiencies through use of artificial intelligence, machine learning, natural language processing.

Organization



OPP Organizational Structure

Statutes



Legislative Mandate (Priority):

- **Requires** EPA to screen pesticide chemicals for their potential for estrogenic effects in humans

Discretionary Authority:

- Authorizes EPA to include other endocrine effects similar to an estrogen effect (expanded to androgen and thyroid)
- Addresses human health (expanded to include aquatic and terrestrial vertebrate wildlife)
- Authorizes EPA to screen any other substances similar to a pesticide chemical

Endocrine Disruptor Definition

2002 World Health Organization (WHO)
definition of “endocrine disruptor”

An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

Tiered Testing

EDSP's tiered approach to screen chemicals includes a Tier 1 battery of assays and Tier 2 tests.

Tier 1:

- 5 *In vitro* and 6 *in vivo* screens
- Detect **potential to interact** with endocrine system

Tier 2:

- May be called in after Weight of Evidence (WoE) review of Tier 1 data
- Multi-life stage/generational studies covering a broad range of taxa
- Determine **adverse apical outcomes** associated with endocrine effects

EDSP Tier 1 Battery	Type	Tier 1 Test Guideline
Estrogen Receptor (ER) Binding	In vitro	OCSPP 890.1250
Estrogen Receptor Transactivation (ERTA)	In vitro	OCSPP 890.1300
Uterotrophic (UT)	In vivo	OCSPP 890.1600
Androgen Receptor (AR) Binding	In vitro	OCSPP 890.1150
Aromatase	In vitro	OCSPP 890.1200
Steroidogenesis (STR)	In vitro	OCSPP 890.1550
Hershberger	In vivo	OCSPP 890.1400
Female Rat Pubertal	In vivo	OCSPP 890.1450
Male Rat Pubertal	In vivo	OCSPP 890.1500
Fish Short Term Reproduction (FSTRA)	In vivo	OCSPP 890.1350
Amphibian Metamorphosis (AMA)	In vivo	OCSPP 890.1100

EDSP Tier 2 Tests	Type	Tier 2 Test Guideline
Rat 2-generation Reproduction	In vivo	OCSPP 870.3800
Rat Extended 1-Gen Reproduction	In vivo	OECD TG 443
Medaka Extended 1-Gen Reproduction	In vivo	OCSPP 890.2200
Larval Amphibian Growth & Development	In vivo	OCSPP 890.2300
Avian Multi-Generation Reproduction	In vivo	OCSPP 890.2100

https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-890-endocrine-disruptor-screening-program

Lists of Chemicals

EDSP screens pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen, and thyroid hormone systems. Designation on List 1 or List 2 does **not** mean a chemical will affect the endocrine system.

First List of Chemicals for Tier 1 Screening (List 1) announced in 2009

- High exposure potential
  - Pesticide active ingredients
  - High Production Volume (HPV) chemicals used as pesticidal inert ingredients
- 67 chemicals on original list
- 15 chemicals were not supported by industry
- 52 chemicals were tested in Tier 1 battery

Second List of Chemicals for Tier 1 Screening (List 2) announced in 2013

- Identified via EPA's drinking water and pesticide programs
  - Excluded biologic agents, naturally-occurring chemicals, and hormones
- 107 chemicals
- Approximately 60 chemicals are not pesticide chemicals

Universe of Chemicals

EDSP published a Universe of Chemicals list in 2012.

The updated list of chemical substances covered by the EDSP include:

~ 1,200 pesticide active ingredients,

~ 2,500 pesticide inert ingredients,

} Statutorily Required: FFDCA§408(p)(3)(A)

~ 6,000 drinking water contaminants,

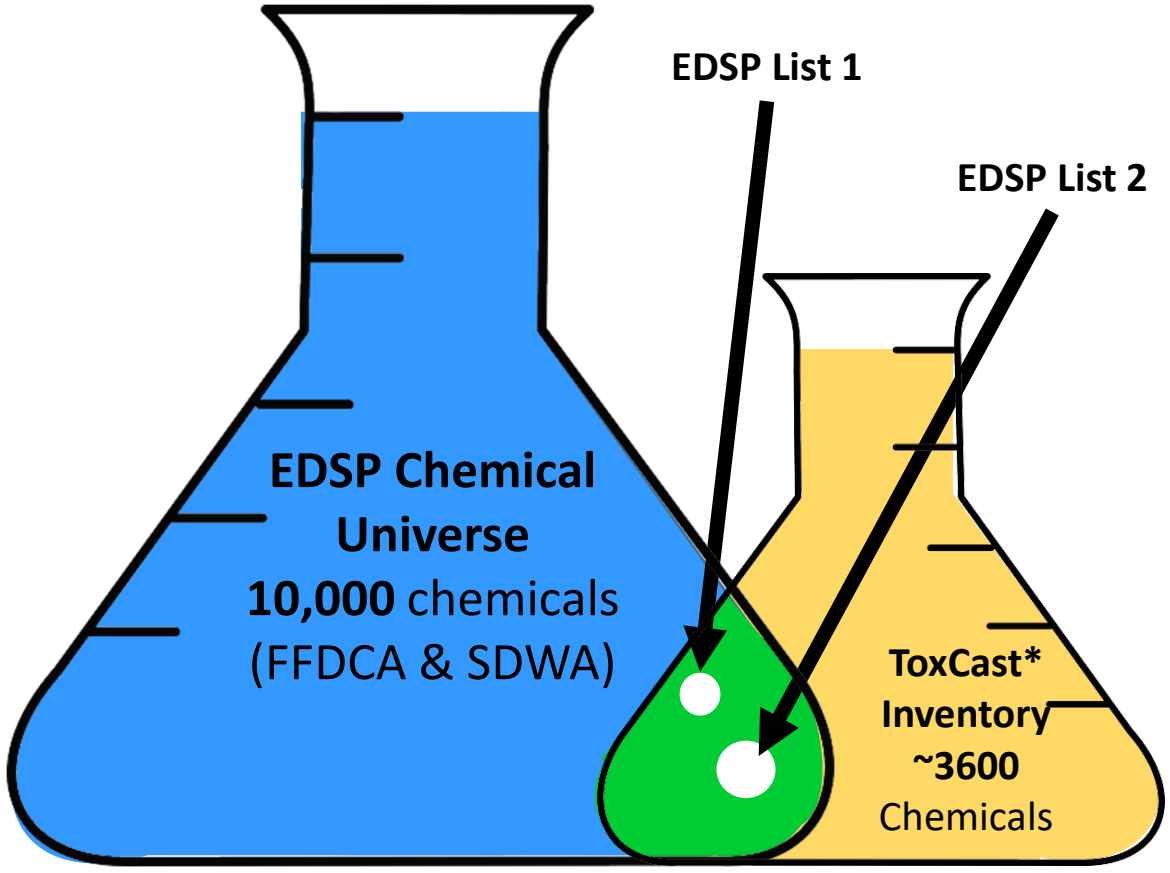
} Discretionary Authority: SDWA§1457

with some overlap between these lists.

https://www.epa.gov/endocrine-disruption/universe-chemicals-potential-endocrine-disruptor-screening-and-testing

EDSP's Evolution: New Approach Methods (NAMs)

- Rapidly **screen** chemicals in the EDSP Universe for endocrine bioactivity
- Provide **alternative data** for specific endpoints in the EDSP Tier 1 battery of assays
- Contribute to the **weight of evidence** screening level determination of a chemical's potential bioactivity



* ToxCast is the Toxicity Forecaster developed by US EPA

Need for Alternative Methods

Goal: Thousands of chemicals to be screened as quickly and accurately as possible.

New Approach Methods (NAMs) are being developed for enhancing efficiencies.

High-Throughput (HTP) Assays for

- Estrogen Receptor, Androgen Receptor, Steroidogenesis, Thyroid Pathway

Other tools and approaches

- SeqAPASS, Systematic Reviews, In Vitro to In Vivo Extrapolation (IVIVE), and Bioactivity Exposure Ratio (BER)

In January 2023, EPA published a draft paper on the availability of NAMs for EDSP.

https://www.regulations.gov/document/EPA-HQ-OPP-2021-0756-0002

Validated Alternatives
ER and AR Full Pathway Models

Estrogen Receptor (ER) pathway model may be used as an alternative to performing three current EDSP Tier 1 screening assays:

- ER binding *in vitro* assay (OCSPP 890.1250)
- ER transcriptional activation (ERTA) *in vitro* assay (OCSPP 890.1300)
- *In vivo* Uterotrophic assay (rat) (OCSPP 890.1600)

Androgen Receptor (AR) pathway model may be used as an alternative for one current EDSP Tier 1 screening assay:

- AR binding *in vitro* assay (OCSPP 890.1150)

EDSP Tier 1 Battery	Type	Tier 1 Battery Alternatives
Estrogen Receptor (ER) Binding	In vitro	ER Model (Alternative)
Estrogen Receptor Transactivation (ERTA)	In vitro	ER Model (Alternative)
Uterotrophic (UT)	In vivo	ER Model (Alternative)
Androgen Receptor (AR) Binding	In vitro	AR Model (Alternative)
Aromatase	In vitro	STR Model (Future)
Steroidogenesis (STR)	In vitro	STR Model (Future)
Hershberger	In vivo	AR/STR Model (Future)
Female Rat Pubertal	In vivo	ER, STR, THY Models (Future)
Male Rat Pubertal	In vivo	AR, STR, THY Models (Future)
Fish Short Term Reproduction (FSTRA)	In vivo	ER, AR, STR Models (Future)
Amphibian Metamorphosis (AMA)	In vivo	THY Model (Future)
EDSP Tier 2 Tests	**Type**	**Tier 2 Test Alternatives**
Rat 2-generation Reproduction	In vivo	ER, AR, STR, THY (Future)
Rat Extended 1-Gen Reproduction	In vivo	ER, AR, STR, THY (Future)
Medaka Extended 1-Gen Reproduction	In vivo	ER, AR, STR (Future)
Larval Amphibian Growth & Development	In vivo	THY (Future)
Avian Multi-Generation Reproduction	In vivo	ER, AR, STR, THY (Future)

High Throughput and Computational Methods

ER Full Pathway Model

Use multiple assays (18) for pathway coverage

- Different technologies
- Different points in pathway

No assay is perfect

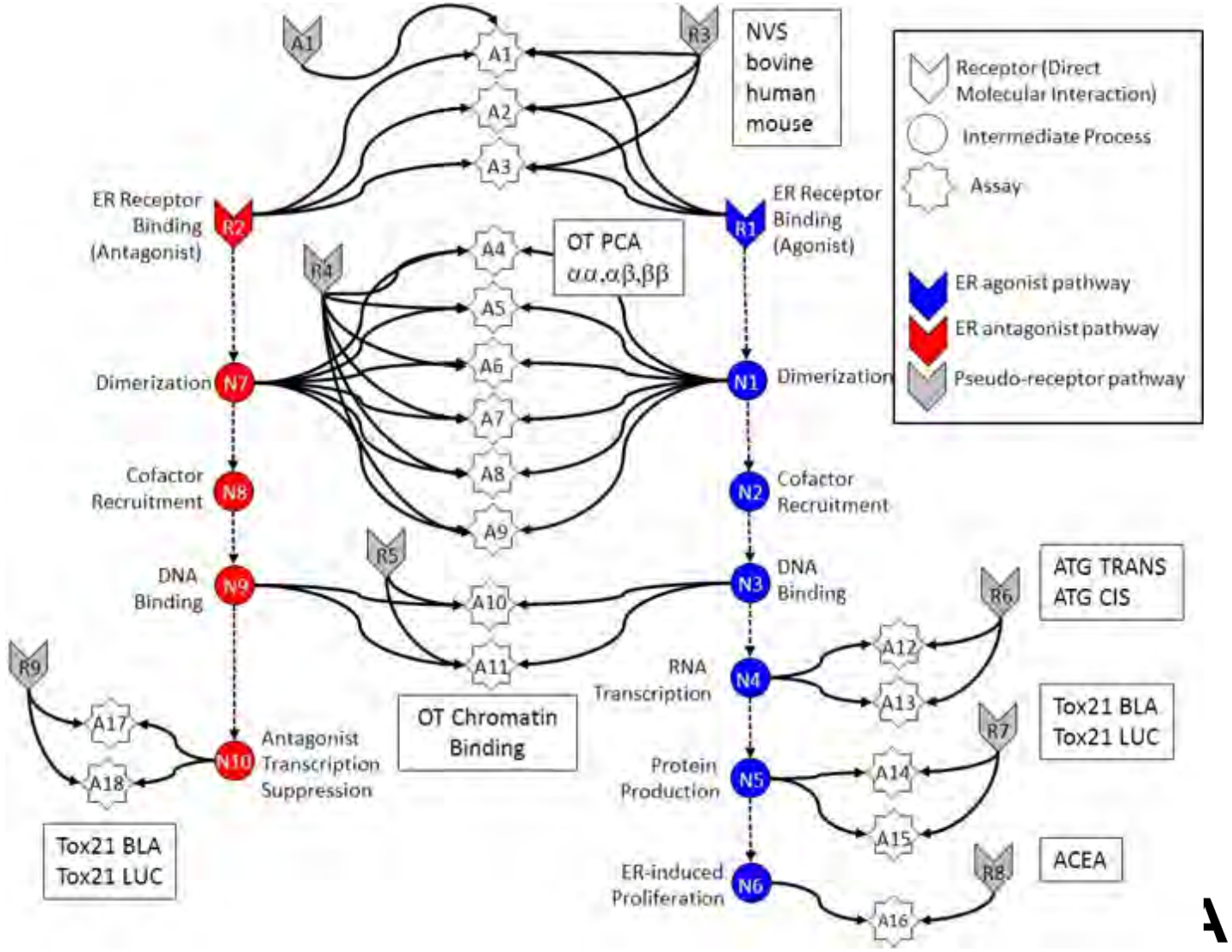
- Assay Interference
- Noise

Use model to integrate assays

Evaluate model against reference chemicals

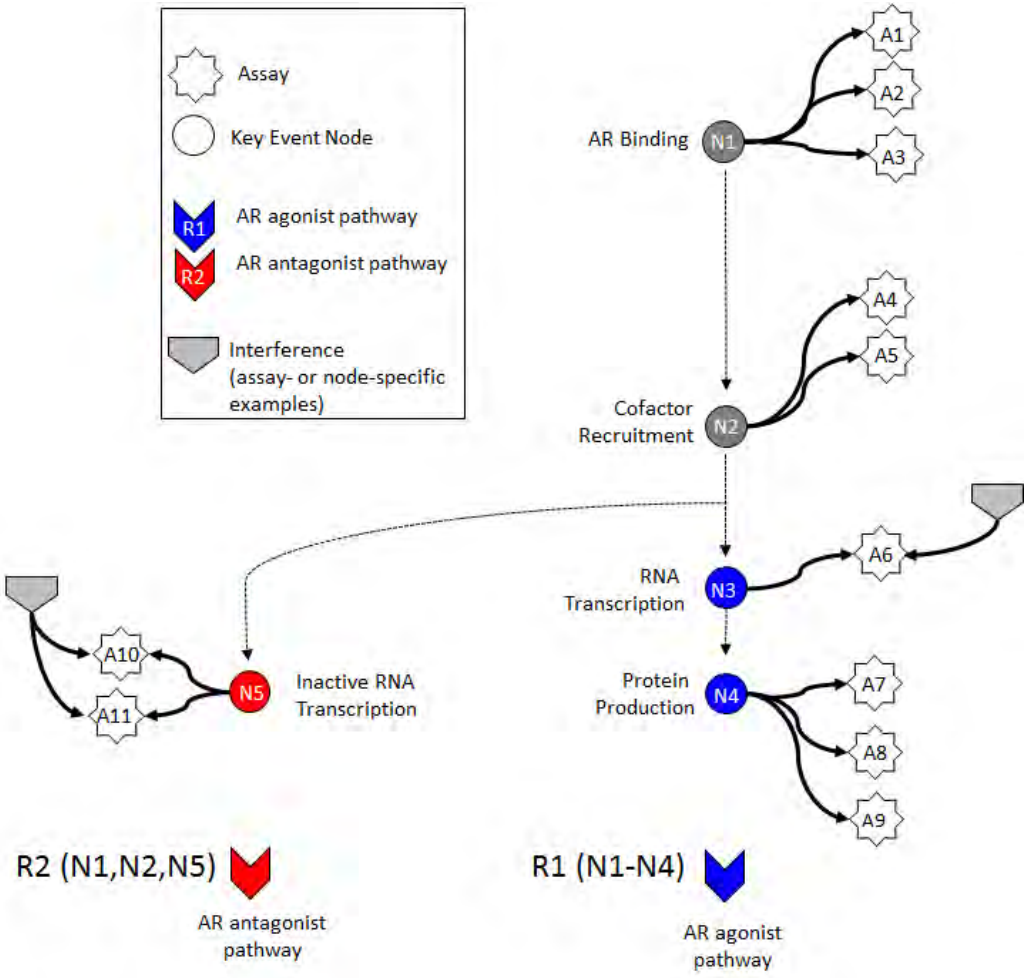
Methodology being applied to other pathways

US EPA. 2014. FIFRA SAP "Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

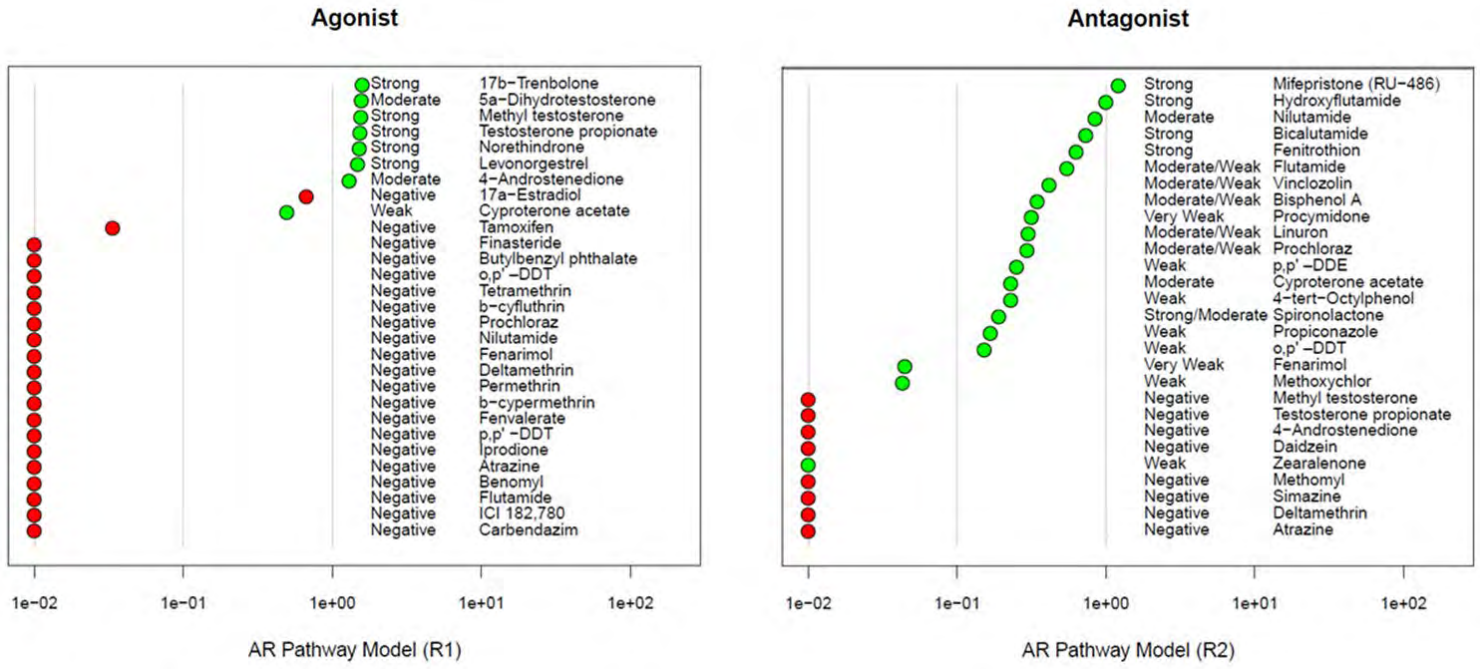


High Throughput and Computational Methods

AR Full Pathway Model



AR Reference Chemical Performance



US EPA. 2017. FIFRA SAP "Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Bioactivity, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways"

Other NAMs

The following NAMs are proposed for use in **priority setting** or as **Other Scientifically Relevant Information (OSRI)** in WoE evaluations:

- Reduced assay subset (4-7 assays) ER & AR pathway models
- QSAR models for ER and AR
- SeqAPASS – Sequence Alignment to Predict Across Species Susceptibility tool
- IVIVE – In Vitro to In Vivo Extrapolation
- iBER – integrated Bioactivity and Exposure Ratio

Tools for Future Development

- Steroidogenesis HT assay
- Thyroid Adverse Outcome Pathway Network

ER and AR Subset Models

The full ToxCast ER and AR pathway models are proposed as **alternatives** to Tier 1 assays

- BUT expensive, and some component assays no longer commercially available

Can we simplify?

- Assay subsets were assessed, and 4 to 7 assays provided equivalent performance (*e.g.*, balanced accuracy) to the full pathway models

Next steps

- V**alidate assay subsets** (4 - 5 assays per pathway) using reference chemicals and a set of 'validation' chemicals
- Once validated, screening of pesticide chemicals will begin using these subsets

ER Subset Models

Assay #	ER Assay type	Species
1	receptor binding	bovine
2	receptor binding	human
3	receptor binding	mouse
4	receptor dimerization	human
5	receptor dimerization	human
6	receptor dimerization	human
7	receptor dimerization	human
8	receptor dimerization	human
9	receptor dimerization	human
10	DNA binding	human
11	DNA binding	human
12	transcriptional activity	human
13	transcriptional activity	human
14	gene expression	human
15	gene expression	human
16	cell proliferation	human
17	gene expression	human
18	gene expression	human

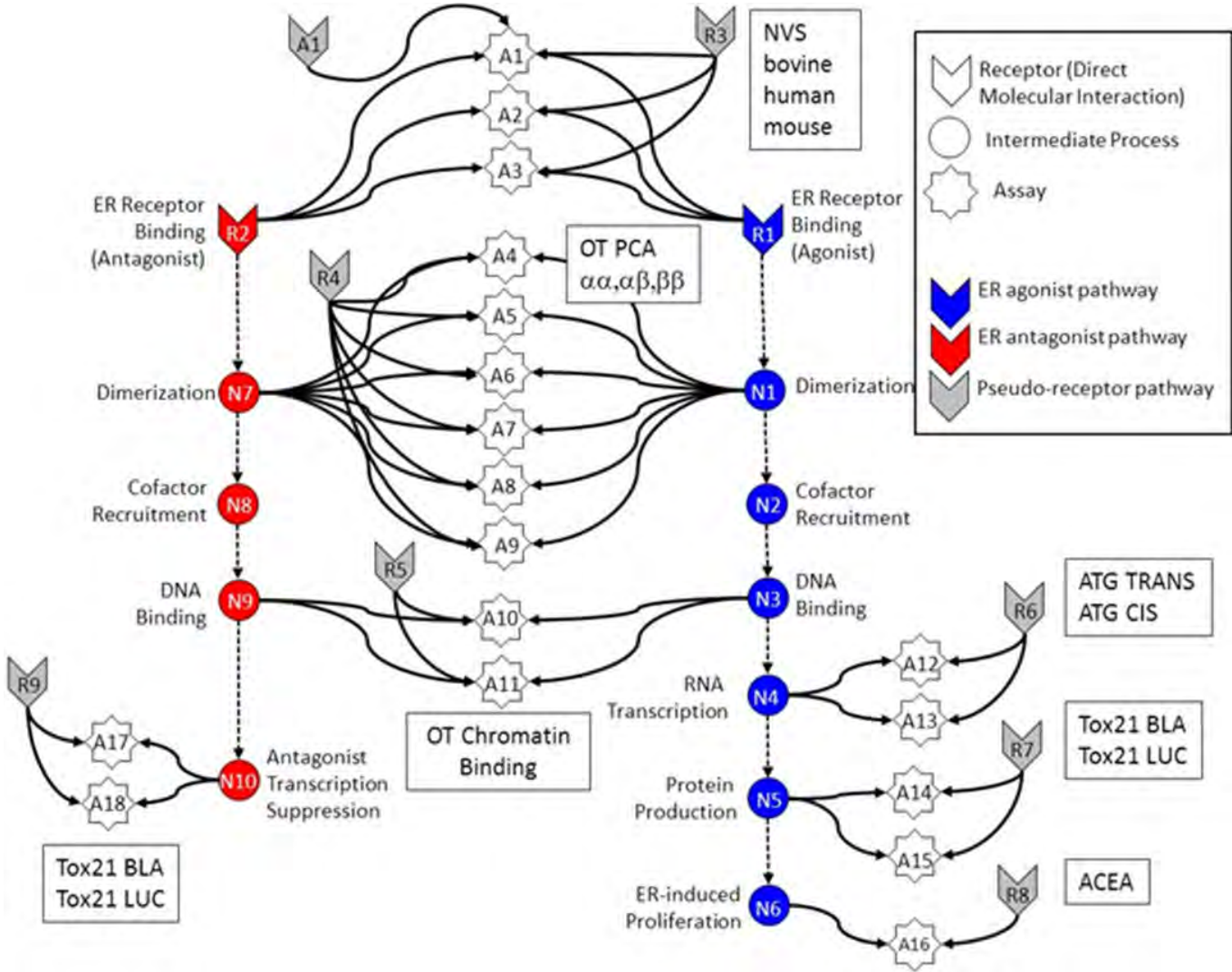
Key events

Binding

Dimerization

Transactivation

Proliferation



Endocrine Disruptor Science Policy Council (EDSPOC)

OPP established the EDSPOC in 2022 to make recommendations concerning

- FFDCA section 408(p)(4) **exemptions**
- When the use of validated **NAMs** as alternatives is acceptable
- Appropriate use of **OSRI** for use in a weight-of-evidence (WoE) analysis
- Assist in reviewing registrant-submitted rebuttals

Regularly scheduled meetings with 13 members consisting of two co-chairs, one secretary, nine other members and the OPP Senior Science Advisor.

EDSPOC will play a key role in ensuring continued progress in implementing EDSP.

EDSP Exemptions

Under FFDCA, EPA can exempt chemicals from the Endocrine Disruption Screening Program

Sufficient information to conclude that a chemical is anticipated not to produce an effect in humans or other organisms similar to an effect produced by a naturally occurring estrogen, androgen or thyroid hormone

Exemptions (8) have previously been issued for chemicals with limited use patterns and therefore limited potential for exposure and for chemicals with limited or targeted toxic effects

- *Exposure examples*: Acetominophen (2014) and Gonadatropin Releasing Hormone (2020)
- *Limited toxicity examples*: Agrobacterium Radiobacter strains K84 and K1026 (2012), Dioctyl Sodium Sulfosuccinate (DSS; 2014) and Undecylenic Acid (UDA; 2014), Polybutene Resin (2014), Kaolin (2015)

Since approval of the charter in 2022, EDSPOC has approved an additional 6 exemptions.

Other Progress

Program Management

- Established EDSPOC
- Developed coordination memo with Office of Water
- More frequently updating EDSP website (epa.gov/endocrine-disruption)
- Hired Senior Advisor to coordinate regulatory implementation (*that's me!*)

EDSP NAMs Paper

- Draft released January 2023
- Will release final paper following resolution of comments
- Includes Response to Comments on 2015 "Pivot" Notice and 2017 FIFRA SAP

EDSP Targeted Goals

2023

- Publish the EDSP NAMs Paper (January 19, 2023)
- Develop an EDSP strategic plan with implementation and performance measures
- Determine and publish need for List 1 Tier 2 data

2024

- Publish List 2 action plan
- Evaluate inclusion of Tier 1 in Part 158 registration

2025

- Initiate any List 1 Tier 2 test orders

Thank you!

Questions?

Contact: Aubee.catherine@epa.gov
Catherine Aubee, Senior Advisor
Endocrine Disruptor Screening Program
U.S. Environmental Protection Agency

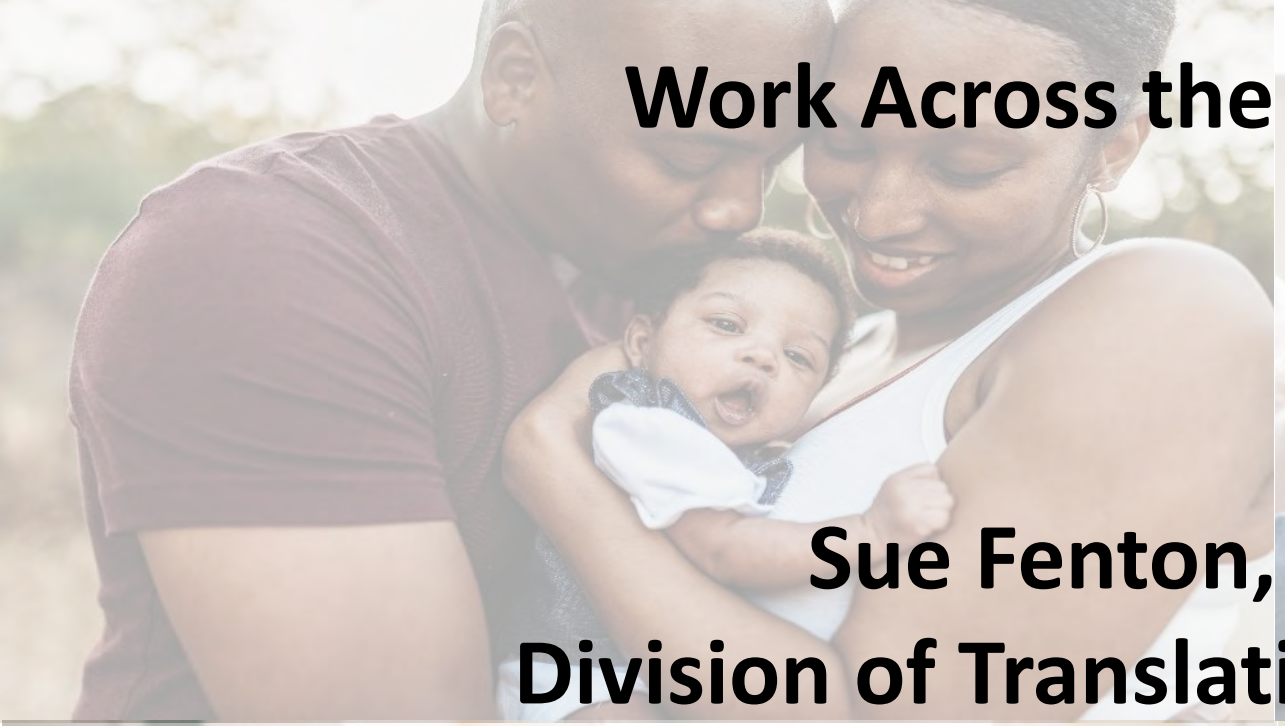
EPA

Work Across the Government

Sue Fenton

Reproductive Endocrinology Lead

NIEHS National Toxicology Program




Work Across the Government

Sue Fenton, PhD MS
Division of Translational Toxicology
- NIEHS -

July 19, 2023

Endocrine Disrupting Chemicals and Women's Health Symposium

National Institute of Environmental Health Sciences
Your Environment. Your Health.

The National Institute of Environmental Health Sciences

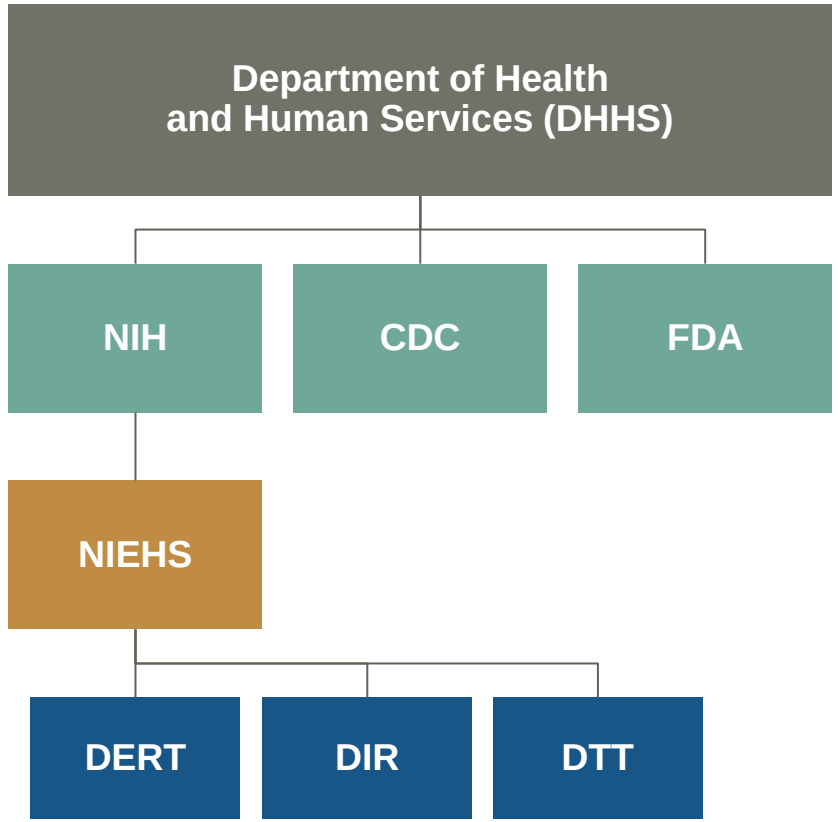
MISSION Discover how the environment affects people in order to promote healthier lives

VISION Provide global leadership for innovative research that improves public health by preventing disease and disability

Division of Extramural Research & Training (DERT)
- *Plans, directs, and evaluates grant programs that support research in environmental health*

Division of Intramural Research (DIR)
- *Carries out fundamental research in NIEHS laboratories to investigate the biological mechanisms that underlie response to environmental stressors*

Division of Translational Toxicology (DTT)
- *Evaluates chemicals/agents of public health concern by developing and applying tools of modern toxicology and molecular biology*

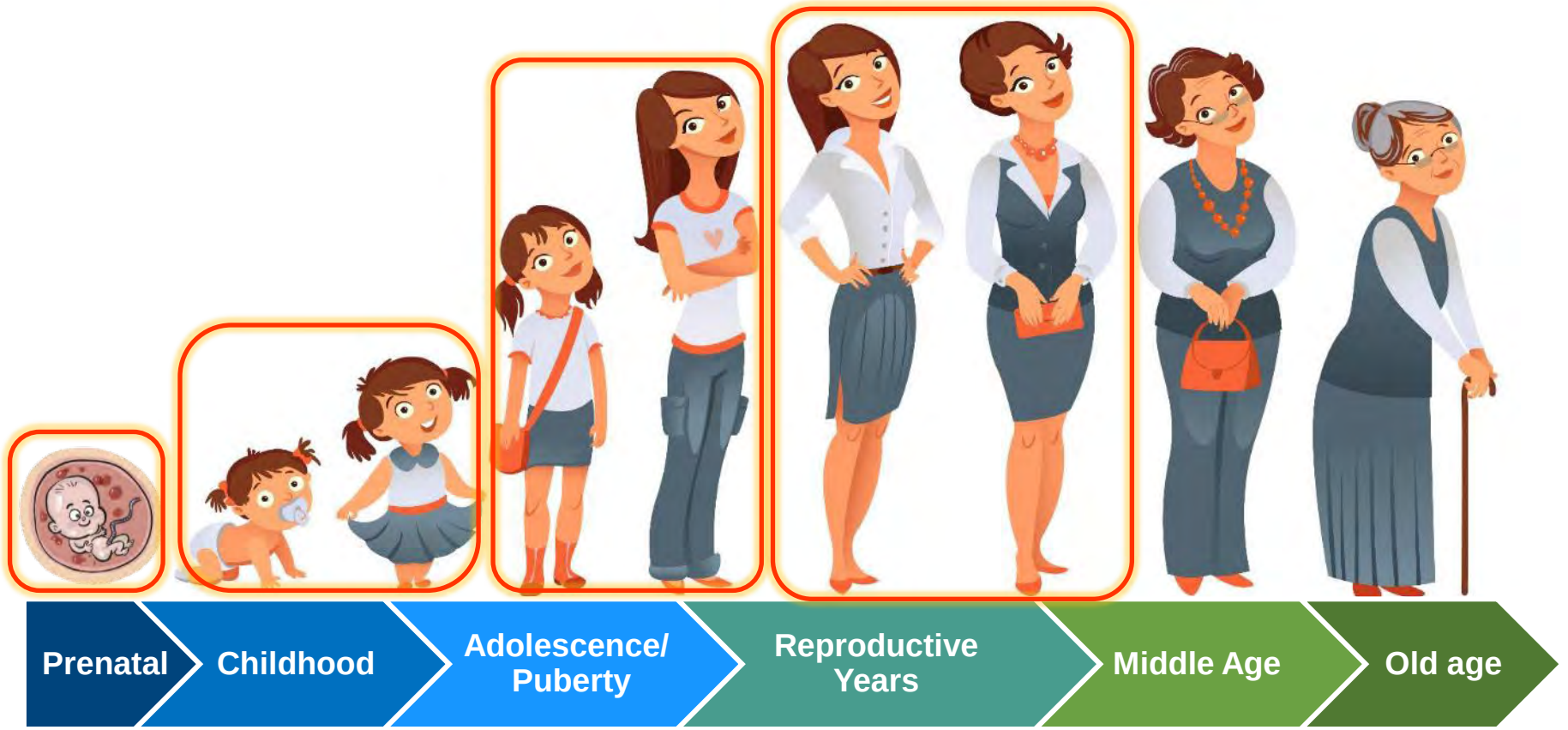


NIEHS: DES and Environmental Estrogens

- 1940's-71: DES prescribed to millions of women to reduce miscarriage; also given to suppress milk production, reduce hot flashes, stunt growth in "tall" girls, treat acne, etc…
- McLachlan, Korach, & Newbold reported:
  - Exposure to exogenous estrogens during fetal development will profoundly alter sexual differentiation (1975 and onward)
  - DES is a transplacental carcinogen
  - Developmental exposure to DES can cause obesity in offspring
- "Environmental Estrogens"
  - Certain chemicals can act like or interfere with hormones

John McLachlan

Windows of Susceptibility



Fenton SE. Endocrine-disrupting compounds and mammary gland development: early exposure and later life consequences. Endocrinology. 2006 Jun;147(6 Suppl):S18-24. doi: 10.1210/en.2005-1131.

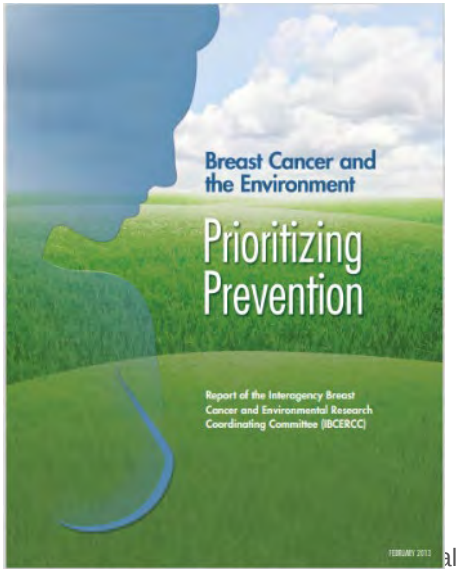
EDC's and Women's Health

- **Maternal Health**
- **Infertility**
- **Puberty and development**
- **Endometriosis, uterine fibroids, ovarian dysfunction, and lactational defects**
- **Premature menopause**
- **Breast, ovarian, cervical, and endometrial cancer**

Breast Cancer & the Environment Research Program (BCERP)

- **2004-2019 Multi-Center**
- **DOHaD approach**
- **Evaluation of multiple EDCs**
- **Puberty timing**
- **Mammographic density**
- **Breast outcomes**

- **Hundreds of publications**



NIEHS Initiatives in DOHaD Research

- Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes and Metabolic Syndrome
- Preconception and Transgenerational Inheritance programs - EDCs
- The Role of the Microbiome in DOHaD program
- Environmental influences on Placental Origins of Development (ePOD) program
- Maternal Health program
- Children's Environmental Health programs
  - NIEHS/EPA Children’s Centers
  - CHEAR/HHEAR
  - ECHO

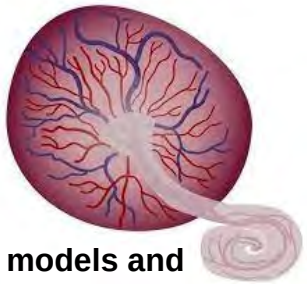
Jerry Heindel

Thad Schug

Heindel – founding member
U.S. DOHaD Society

Current EDC Programs

Environmental Influences on Placental Origins of Development (ePOD) Program (2014-current)



- Accelerate development and application of new models and methods for placental assessment
- Better understand the effects of exposures on early stage placental physiology, endocrine, immune, and metabolic functions
- Determine relationships between exposures, placental health, and subsequent effects on fetal and maternal health

Pregnancy as a Vulnerable Time Period for Women's Health (2020 – current)

- Program Goal: spur animal-based mechanistic and epidemiological research to investigate exposures during pregnancy and the postpartum period with impacts on maternal health and determine the life-long effects of on a woman's health
- Research includes a range of exposures and outcomes impacting women's health up to 12 years post partum
  - PFAS, PCBs, pesticides, flame retardants, PM2.5, phthalates, phenols/parabens, PAHs, metals
  - Cardiometabolic biomarkers and type 2 diabetes, weight retention and adiposity, atherosclerosis and cardiovascular health, immune cell function, endocrine function, and bone health

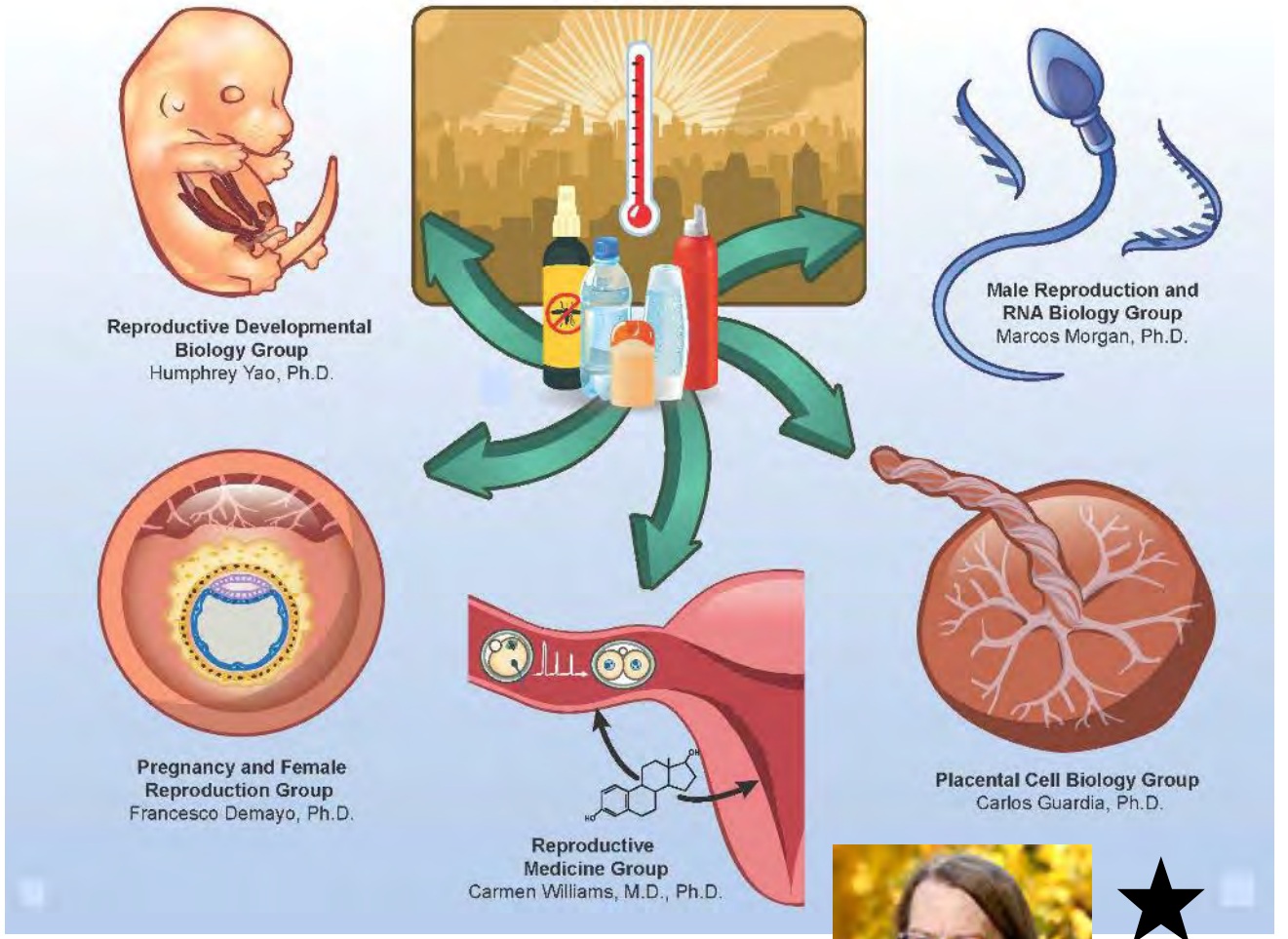
Preconception Exposure Program (2017- current)

- Work in established animal model systems
- Pre-fertilization exposures, NOT *in utero*, or post-conception
- Comprehensive mechanistic analysis
- Environmentally-induced germ cell alterations
- Endocrine disruptors, pesticides, components of air pollution, combined exposures, etc
- Studies should focus on link between exposure and health outcomes in first generation offspring

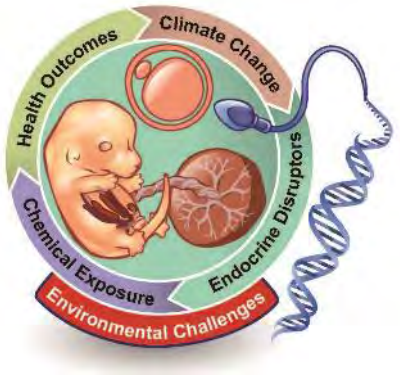
Thad Schug, PhD Abee Boyles, PhD

National Institute of Environmental Health Sciences
Your Environment. Your Health.

Reproductive and Developmental Biology Laboratory



★



RDBL
REPRODUCTIVE & DEVELOPMENTAL BIOLOGY LABORATORY

★

The Sister Study

Enrolled over 50,000 women with a sister with breast cancer (2004-2009) to address concerns about environmental exposures

- Sisters have 2-fold breast cancer risk
- Increased power to detect associations
- Sisters highly motivated; response rates high

> 4,000 incident breast cancer cases

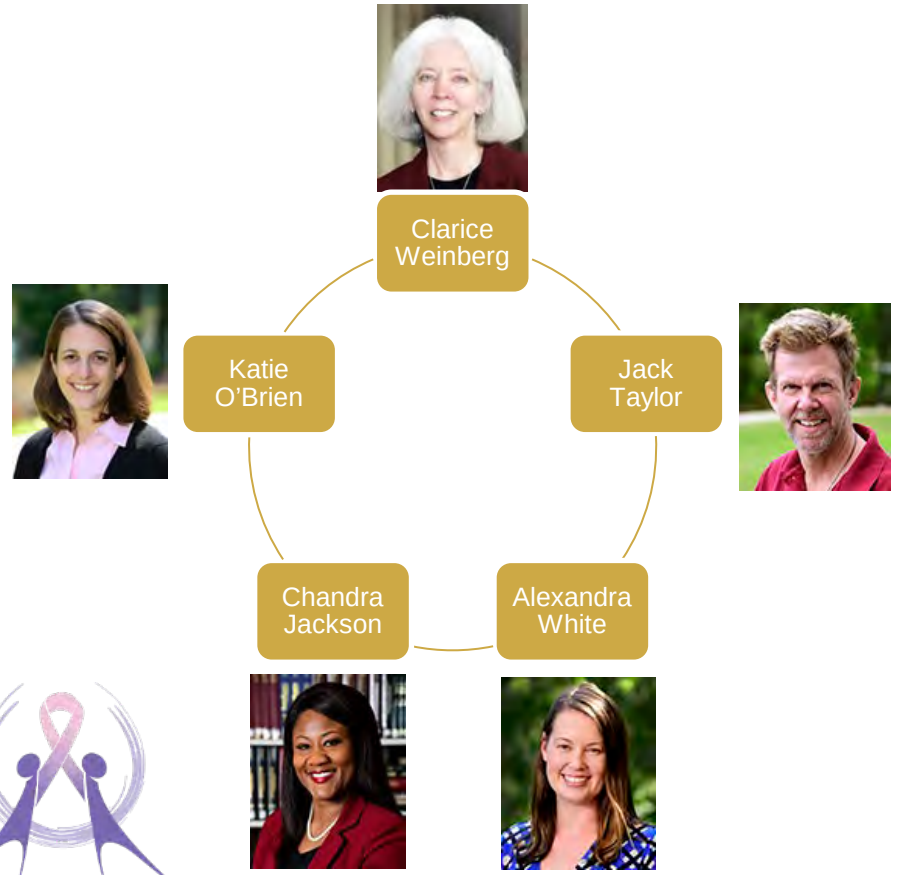
- Ongoing follow-up
- Able to consider breast cancer subtypes and population subgroups

Range of health outcomes & exposures, including EDCs

- Hormone responsive cancers (e.g., ovary, uterus, thyroid)
- Metabolic dysfunction and disease
- Exposomics, genomics, GIS-linkages, biomarkers, questionnaire data

Sandler et al., EHP 2017

Sister Study Co-investigators



THE SISTER STUDY
BREAST CANCER RESEARCH

National Institute of Environmental Health Sciences
Your Environment. Your Health.

Hair Straightener/Relaxers and Uterine Cancer Incidence

Background: Hair straightener/relaxers contain endocrine-disrupting chemicals, can release formaldehyde when heated

- Frequent use of straighteners/relaxers associated with breast and ovarian cancer *(Eberle et al., 2020 IJC, White et al., 2021 IJC, White et al., 2020 Carcinogenesis)*

Hypothesis: Chemical hair product use is associated with a higher uterine cancer incidence

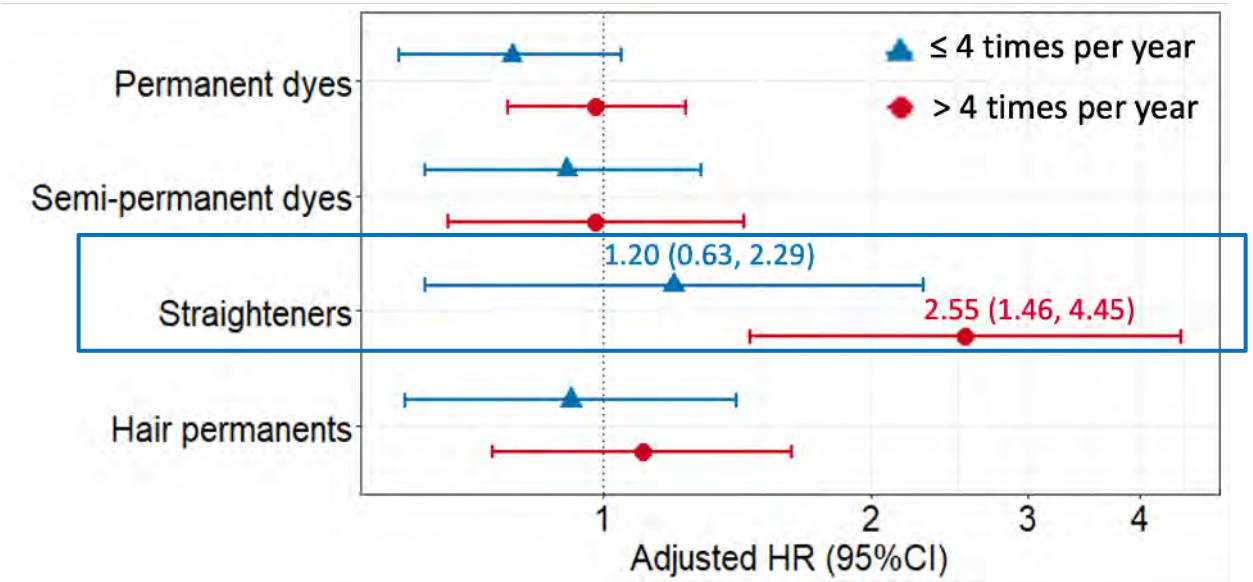
Methods: Sister Study participants with a uterus at enrollment (N=33,497, 2003-2009)

- Self-reported frequency of hair products use in <12 months; proxy for "usual adult use"
- ~10.9 years of follow-up
- N=378 uterine cancer cases

Lexie White, PhD

Results:

Frequent hair straightener/relaxer use (>4 times/year) associated with uterine cancer



- **Black women were 60% of ever users**
- **Associations similar for Black and Non-Hispanic White women**

Conclusion: Frequent hair straighteners/relaxer users were **more than twice as likely** to develop uterine cancer compared to non-users

- Implications may be greater for Black women due to higher prevalence of use

Chang et al, JNCI 2022

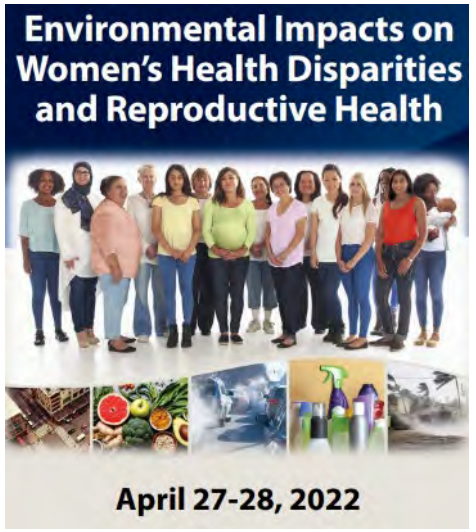
National Institute of Environmental Health Sciences
Your Environment. Your Health.

Health Disparities & U4 Focus

NIEHS Social and Environmental Determinants of Health Initiatives & Programs

EHD-EJ Faculty Website:
https://www.niehs.nih.gov/research/programs/ehd-ej/index.cfm

Workshop Website:
https://www.niehs.nih.gov/news/events/pastmtg/2021/ejworkshop2021/index.cfm



Workshop Website:
https://www.niehs.nih.gov/news/events/pastmtg/2022/ehdworkshop2022/index.cfm

Workshop Website:
https://www.niehs.nih.gov/news/events/pastmtg/2022/eheworkshop2022/index.cfm

Maintaining and Enriching Environmental Epidemiology Cohorts to Support Scientific and Workforce Diversity
U24 Program
RFA Reissue Forthcoming
NOT-ES-23-001
Closed February 10, 2023

Melissa M. Judd-Smarr, PhD

Research to Action: Assessing and Addressing Community Exposures to Environmental Contaminants
R01 Clinical Trial Optional
NIEHS – NIMHD
PAR-22-210
NIH Standard Due Dates

Lindsey Martin, PhD

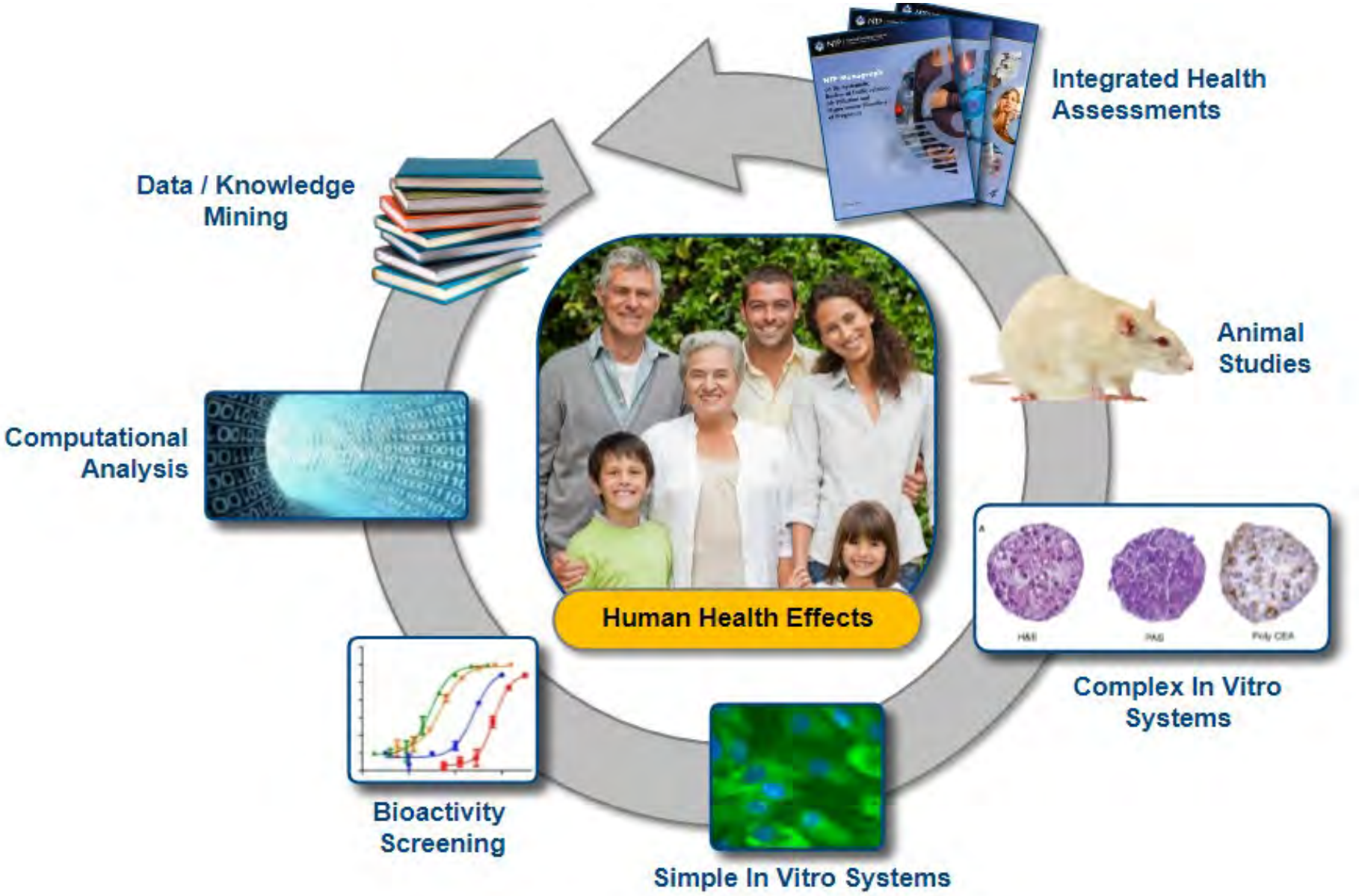
Liam O'Fallon, MA

Website:
https://www.niehs.nih.gov/research/programs/wha/index.cfm

Joan Packenham, PhD

National Institute of Environmental Health Sciences
Your Environment. Your Health.

Translational Toxicology Pipeline



Health Effects Innovation Programs

Exposure-based Research Programs

Responsive Research Programs

Strengthening Capabilities Programs

In utero PFAS exposure sets the stage for a lifetime of increased disease susceptibility

Hypertensive disorders of pregnancy
Adverse birth outcomes
Shortened lactation duration

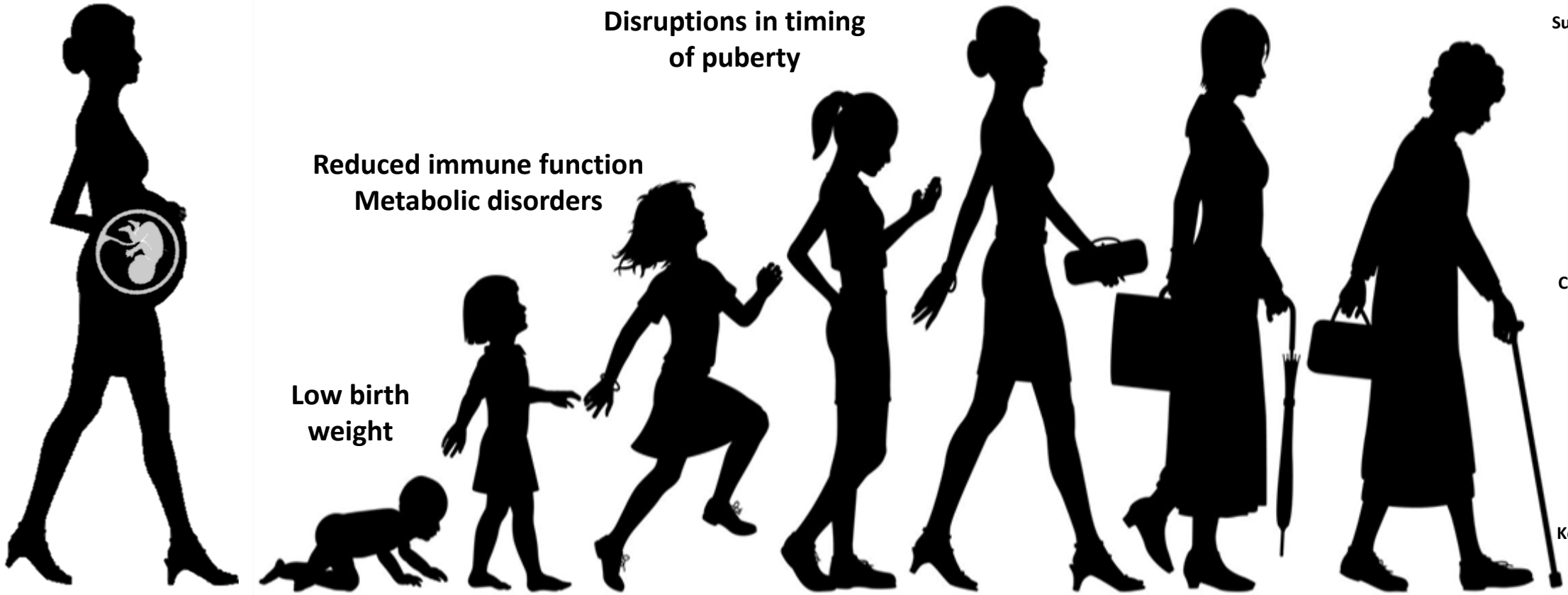
Low birth weight

Reduced immune function
Metabolic disorders

Disruptions in timing of puberty

Menstrual Issues
Reduced fertility

Elevated cholesterol/triglycerides
Reduced kidney function
Thyroid hormone disruption
Cancer



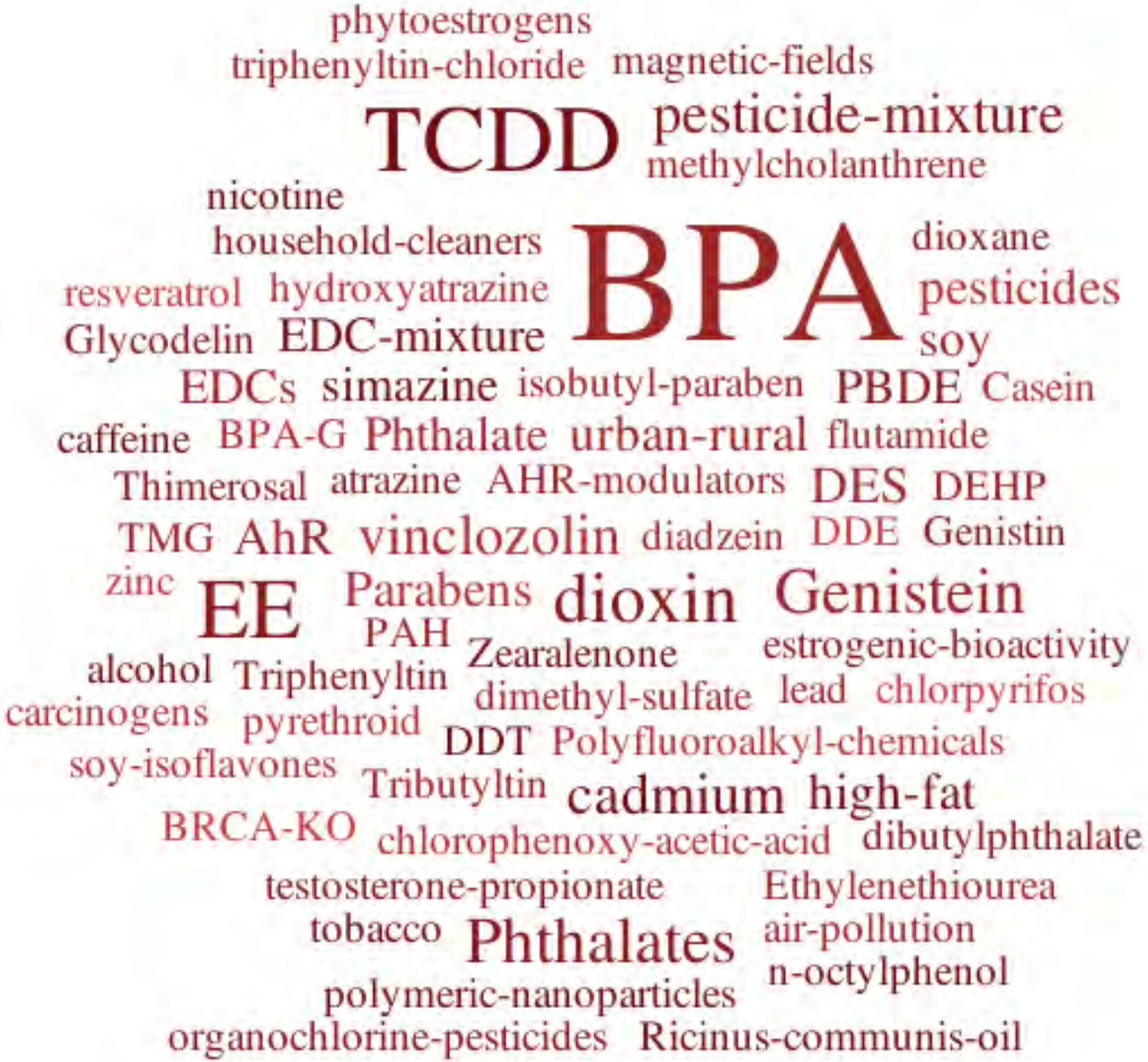
Sue Fenton, PhD MS

Chad Blystone, PhD

Kelly Ferguson, PhD

Thank you for your attention!

Questions??



Work Across the Government

Tucker A. Patterson, Ph.D.

Director

FDA National Center for Toxicological Research

FDA U.S. FOOD & DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Working Across the Government

Tucker A. Patterson, Ph.D.
Director
National Center for Toxicological Research

July 19, 2023

National Center for Toxicological Research

NCTR was established in January 1971 as a non-regulatory national resource to conduct integrated toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health.

PERSONNEL

- 5 Offices
- 6 Research Divisions
- ~500 employees

FACILITY

- > 1M sq. ft. − 30 buildings
- 100+ experimental labs
- 75+ AAALAC labs

Endocrine Disruptor Knowledge Base (EDKB)

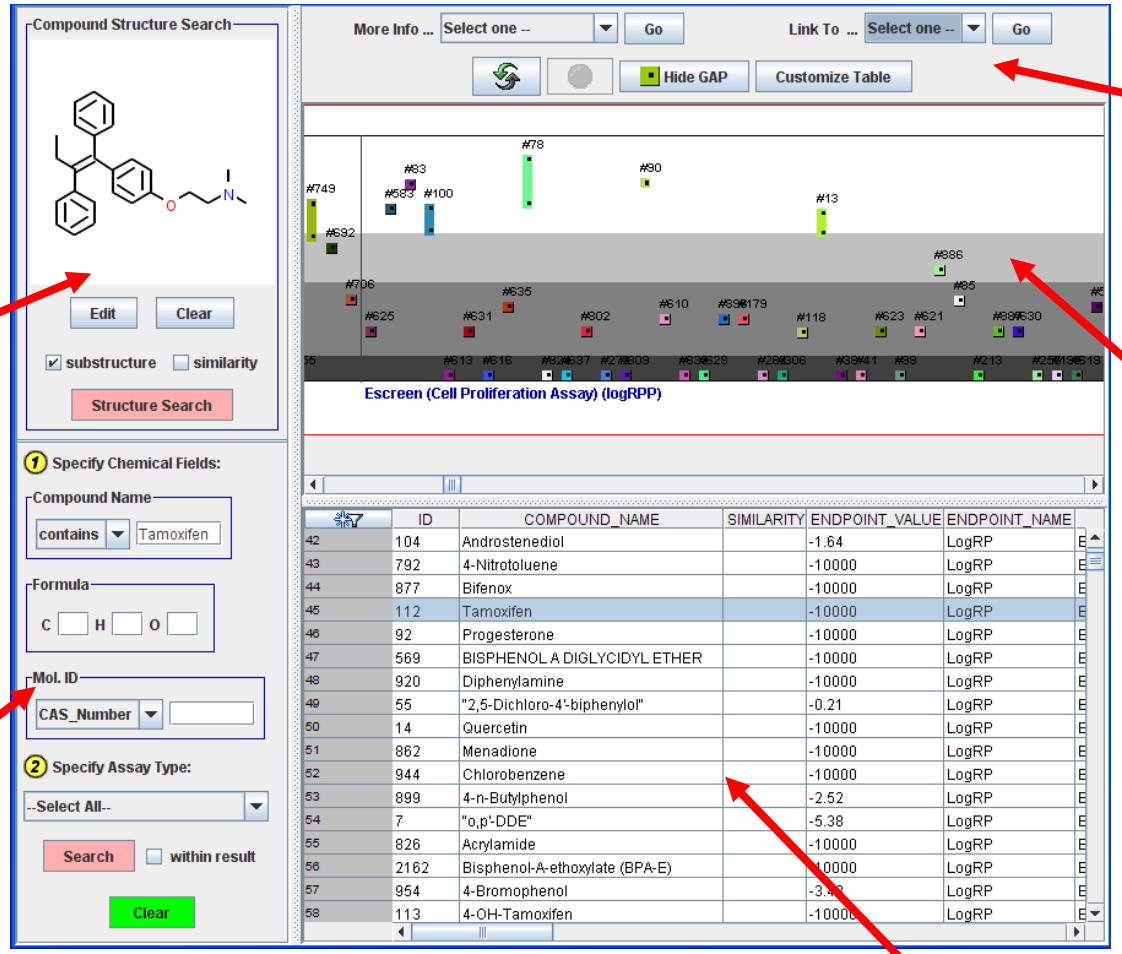
Objective: A resource that contains both experimental data and predictive models for endocrine disrupting compounds

EDKB is intended to serve as a resource for research and regulatory scientists to access endocrine activity data and to foster the development of computational predictive toxicology models. It consists of the following resources:

- a biological activity database
- QSAR (Quantitative Structure-Activity Relationship) training sets
- in vitro and in vivo experimental data for more than 3,000 chemicals
- literature citations
- chemical-structure search capabilities

https://www.fda.gov/science-research/bioinformatics-tools/endocrine-disruptor-knowledge-base-edkb

EDKB – Query and Presentation



Chemical structure & similarity search

Query interface

Link to external resources (e.g., PubChem, ToxNet)

Activity Profile

Excel-like spreadsheet

Estrogenic Activity Database (EADB)

Objective: A resource that contains a comprehensive collection of experimental estrogenic activity data for safety evaluation

Overview:

- Over 18,000 experimental estrogenic data points were curated for more than 8,000 compounds
- Four different types of data (binding, reporter gene, cell proliferation, and in vivo) from 11 species
- In addition to the standardized data and chemical structures, it contains assay protocols, literature references, and chemical properties
- Some SAR/QSAR models have been developed for predicting estrogenic activity

https://www.fda.gov/science-research/bioinformatics-tools/estrogenic-activity-database-eadb

Multigenerational Studies

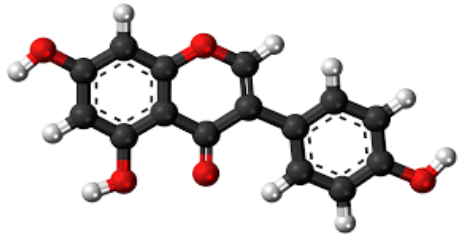
NCTR/NTP Multigenerational Studies

- Studies were initiated under the NIEHS/FDA IAA[1] in 1997 to address certain aspects of the then emerging “endocrine disruptor hypothesis.”
- Broad range of endpoints examined with primary focus on reproductive function and reproductive tract cancers
- Intent was to examine the long-term consequences of doses that produced subtle effects, including doses in the range of human exposures or at levels previously shown to have no or minimal effects in rodent models
- Study design also examined:
  - potential for magnification of subtle reproductive effects over multiple generations
  - importance of exposure windows
  - whether effects are reversible or are imprinted to carry over across generations

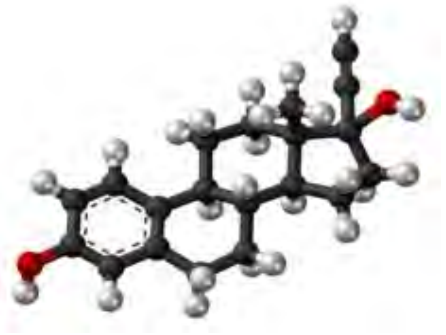
[1]NIEHS/FDA IAA, National Institute of Environmental Health Sciences/US Food and Drug Administration Interagency Agreement

Multigenerational Studies: Test Agents

- Genistein, an isoflavone and phytoestrogen to which there is widespread human exposure through soy foods, dietary supplements, and soy formula
- Ethinyl estradiol (EE_2), a potent synthetic estrogen that is commonly used as the estrogenic component of oral contraceptives
- Pharmacokinetic, neurotoxicology, behavioral, and immunotoxicology studies conducted, in addition to the multigenerational and chronic toxicity studies
- Other compounds with reported effects on estrogen and/or androgen signaling (nonylphenol, methoxychlor, and vinclozolin) also evaluated, although with a more limited scope



Genistein



Ethinyl estradiol

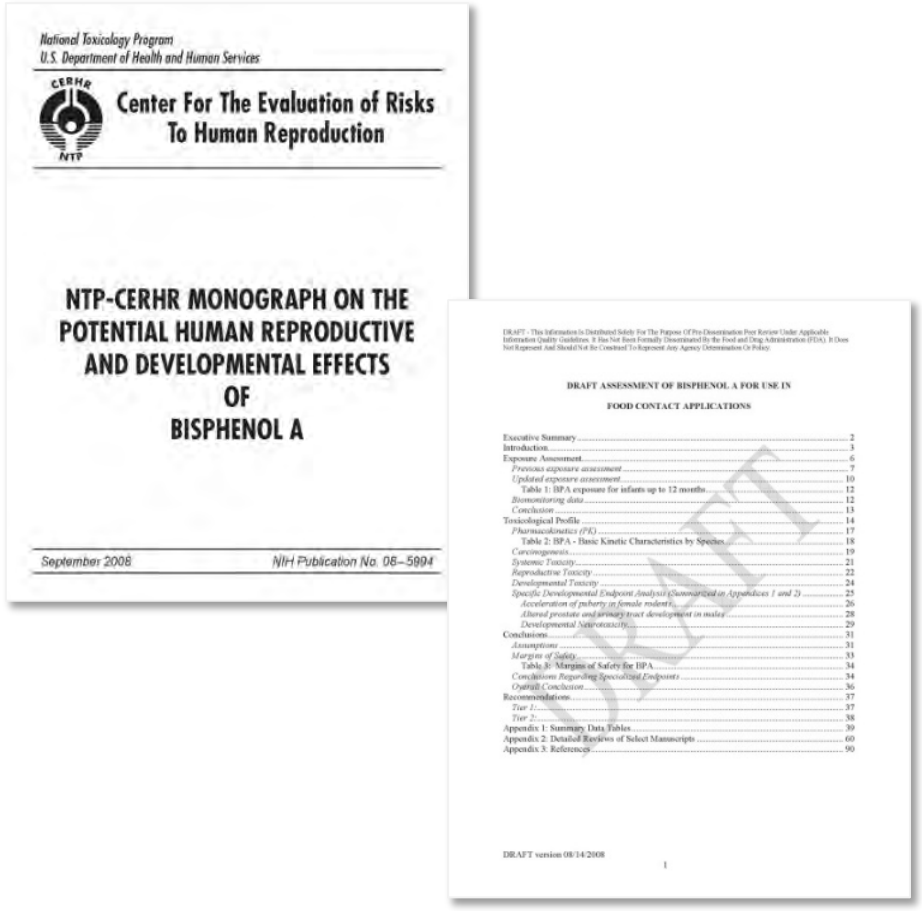
NCTR and NTP Peer-Reviewed Publications

[1]Complete list, [delclos kb newbold r - Search Results - PubMed (nih.gov)]

Bisphenol A (BPA)

- High-production volume industrial chemical
  - Production of polycarbonate plastic and epoxy resins
  - Manufacturing of food and drink storage containers, lining of food cans, dental sealants, medical devices, thermal paper, and optical disks
- Widespread low-level human exposure, mainly oral, due to migration from food packaging materials (indirect food additive)
  - Estimated mean intake range < 0.5 µg/kg body weight/day
- FDA's current assessment is that BPA is safe at the current levels occurring in foods

Back in 2008… Several Data Gaps Identified…



- FDA/NCTR Research Program on BPA was specifically designed to address data gaps identified by the NTP/CERHR[1] and FDA/CFSAN expert reviews, including the need for more research on:
  - Toxicokinetics in various experimental species, over a wide dose range, life stages, and routes of administration
  - Toxicity studies with robust design that include perinatal exposure and internal dosimetry measurements

[1]NTP/CERHR, NTP Center for the Evaluation of Risks to Human Reproduction; FDA/CFSAN, US FDA Center for Food Safety and Applied Nutrition

NCTR Research Program on BPA

Toxicokinetics

- ✓ *Species:* Mouse, rat, non-human primate
- ✓ *Routes of exposure*: Oral, subcutaneous, and intravenous
- ✓ *Life stages:* Fetal, neonatal, juvenile, adult, pregnant
- ✓ *Deuterated BPA* to avoid confounders from environmental BPA

Physiologically based pharmacokinetic (PBPK) models

- ✓ *Extrapolation to humans*
- ✓ *Extrapolation across routes of exposure*
- ✓ *Extrapolation across life stages*

[1]CLARITY-BPA, Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity

Toxicity rat studies

- ✓ *90-day subchronic study*
- ✓ *Two-year chronic study (core study of CLARITY-BPA[1])*
- ✓ Life-long oral exposure, including during gestation
- ✓ Monitoring of BPA and estrogenic background exposures, large sample size, multiple doses and endpoints

NCTR Peer-Reviewed Publications

Toxicokinetic studies

RAPID COMMUNICATIONS IN MASS SPECTROMETRY
Rapid Commun. Mass Spectrom. 2010; **24**: 3011–3020
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/rcm.4733

RCM

Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry†

Nathan C. Twaddle, Mona I. Churchwell, Michelle Vanlandingham and Daniel R. Doerge*

Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, USA

Toxicology and Applied Pharmacology 255 (2011) 261–270

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats

Daniel R. Doerge [a,*], Nathan C. Twaddle [a], Michelle Vanlandingham [a], Ronald P. Brown [b], Jeffrey W. Fisher [a]

[a] Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, USA
[b] Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD, USA

Toxicology and Applied Pharmacology 247 (2010) 158–165

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats

Daniel R. Doerge [a,*], Nathan C. Twaddle [a], Michelle Vanlandingham [a], Jeffrey W. Fisher [b]

[a] Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, USA
[b] Department of Environmental Health Sciences, College of Public Health, University of Georgia, Athens, GA 30602, USA

Toxicology Letters 199 (2010) 372–376

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

ELSEVIER

TL

Lactational transfer of bisphenol A in Sprague–Dawley rats

Daniel R. Doerge*, Michelle Vanlandingham, Nathan C. Twaddle, K. Barry Delclos

Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, United States

Toxicology Letters 211 (2012) 114–119

Contents lists available at SciVerse ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

ELSEVIER

TL

Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice

Daniel R. Doerge*, Nathan C. Twaddle, Michelle Vanlandingham, Jeffrey W. Fisher

Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, United States

Toxicology and Applied Pharmacology 248 (2010) 1–11

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys

Daniel R. Doerge [a,*], Nathan C. Twaddle [a], Kellie A. Woodling [a], Jeffrey W. Fisher [b]

[a] Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, USA
[b] Department of Environmental Health Sciences, College of Public Health, University of Georgia, Athens, GA 30602, USA

Toxicology and Applied Pharmacology 267 (2013) 41–48

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

Concurrent determination of bisphenol A pharmacokinetics in maternal and fetal rhesus monkeys

Tucker A. Patterson [a], Nathan C. Twaddle [b], Cindy S. Roegge [a], Ralph J. Callicott [c], Jeffrey W. Fisher [b], Daniel R. Doerge [b,*]

[a] Division of Neurotoxicology, National Center for Toxicological Research, Jefferson, AR 72079, USA
[b] Division of Biochemical Toxicology, National Center for Toxicological Research, Jefferson, AR 72079, USA
[c] U.S. Food and Drug Administration and Priority One Services Corp, Jefferson, AR 72079, USA

Toxicology Letters 207 (2011) 298–305

Contents lists available at SciVerse ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

ELSEVIER

TL

Pharmacokinetics of Bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and rhesus monkeys

Daniel R. Doerge*, Nathan C. Twaddle, Michelle Vanlandingham, Jeffrey W. Fisher

Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, United States

PBPK models

Toxicology and Applied Pharmacology 257 (2011) 122–136

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

Pharmacokinetic modeling: Prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans

Jeffrey W. Fisher*, Nathan C. Twaddle, Michelle Vanlandingham, Daniel R. Doerge

Food & Drug Administration, National Center for Toxicological Research, Division of Biochemical Toxicology, 3900 NCTR Road, Jefferson, AR 72079, USA

Toxicology and Applied Pharmacology 270 (2013) 45–59

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

Prediction and evaluation of route dependent dosimetry of BPA in rats at different life stages using a physiologically based pharmacokinetic model

Xiaoxia Yang*, Daniel R. Doerge, Jeffrey W. Fisher

Division of Biochemical Toxicology, National Center for Toxicological Research, Food & Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, USA

Toxicology and Applied Pharmacology 289 (2015) 442–456

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

ELSEVIER

CrossMark

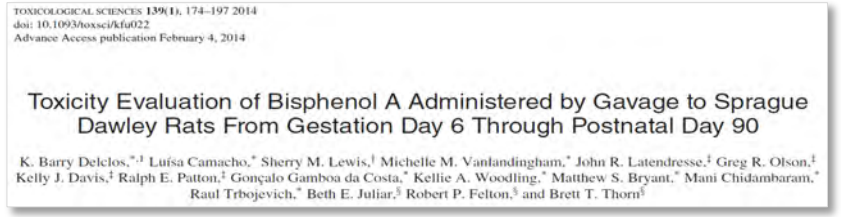
Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A

Xiaoxia Yang [a,*], Daniel R. Doerge [a], Justin G. Teeguarden [b,c], Jeffrey W. Fisher [a]

[a] Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, AR 72079, United States
[b] Health Effects and Exposure Science, Pacific Northwest National Laboratory, Richland, WA 99352, United States
[c] Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, OR 97331, United States

NCTR and NTP Peer-Reviewed Publications

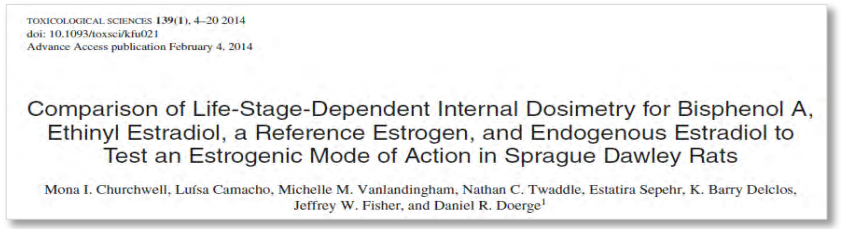
90-day toxicity rat study



TOXICOLOGICAL SCIENCES 139(1), 174–197 2014
doi: 10.1093/toxsci/kfu022
Advance Access publication February 4, 2014

Toxicity Evaluation of Bisphenol A Administered by Gavage to Sprague Dawley Rats From Gestation Day 6 Through Postnatal Day 90

K. Barry Delclos,*,1 Luísa Camacho,* Sherry M. Lewis,† Michelle M. Vanlandingham,* John R. Latendresse,‡ Greg R. Olson,‡ Kelly J. Davis,‡ Ralph E. Patton,‡ Gonçalo Gamboa da Costa,* Kellie A. Woodling,* Matthew S. Bryant,* Mani Chidambaram,* Raul Trbojevich,* Beth E. Juliar,§ Robert P. Felton,§ and Brett T. Thorn§



TOXICOLOGICAL SCIENCES 139(1), 4–20 2014
doi: 10.1093/toxsci/kfu021
Advance Access publication February 4, 2014

Comparison of Life-Stage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague Dawley Rats

Mona I. Churchwell, Luísa Camacho, Michelle M. Vanlandingham, Nathan C. Twaddle, Estatira Sepehr, K. Barry Delclos, Jeffrey W. Fisher, and Daniel R. Doerge[1]

Food and Chemical Toxicology 81 (2015) 92–103

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

ELSEVIER

Effects of oral exposure to bisphenol A on gene expression and global genomic DNA methylation in the prostate, female mammary gland, and uterus of NCTR Sprague-Dawley rats

CrossMark

Luísa Camacho [a,*], Mallikarjuna S. Basavarajappa [a], Ching-Wei Chang [b], Tao Han [c], Tetyana Kobets [a,1], Igor Koturbash [a,2], Gordon Surratt [a], Sherry M. Lewis [d], Michelle M. Vanlandingham [a], James C. Fuscoe [c], Gonçalo Gamboa da Costa [a], Igor P. Pogribny [a], K. Barry Delclos [a]

[a] Division of Biochemical Toxicology, National Center for Toxicological Research, Food and Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, USA
[b] Division of Bioinformatics and Biostatistics, National Center for Toxicological Research, Food and Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, USA
[c] Division of Systems Biology, National Center for Toxicological Research, Food and Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, USA
[d] Office of Scientific Coordination, National Center for Toxicological Research, Food and Drug Administration, 3900 NCTR Road, Jefferson, AR 72079, USA

Chronic toxicity rat study (CLARITY-BPA core study)

Food and Chemical Toxicology 132 (2019) 110728

Contents lists available at ScienceDirect

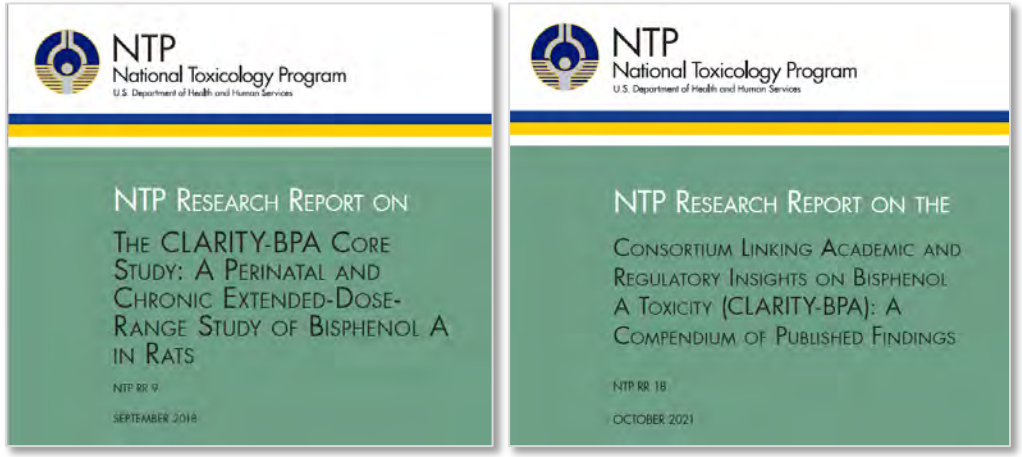
Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

ELSEVIER

A two-year toxicology study of bisphenol A (BPA) in Sprague-Dawley rats: CLARITY-BPA core study results

L. Camacho[a], S.M. Lewis[a], M.M. Vanlandingham[a], G.R. Olson[b], K.J. Davis[b], R.E. Patton[b], N.C. Twaddle[a], D.R. Doerge[a], M.I. Churchwell[a], M.S. Bryant[a], F.M. McLellen[a], K.A. Woodling[a], R.P. Felton[a], M.P. Maisha[a], B.E. Juliar[a], G. Gamboa da Costa[a], K.B. Delclos[a,*]



NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP RESEARCH REPORT ON THE CLARITY-BPA CORE STUDY: A PERINATAL AND CHRONIC EXTENDED-DOSE-RANGE STUDY OF BISPHENOL A IN RATS

NTP RR 9

SEPTEMBER 2018

NTP
National Toxicology Program
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NTP RESEARCH REPORT ON THE CONSORTIUM LINKING ACADEMIC AND REGULATORY INSIGHTS ON BISPHENOL A TOXICITY (CLARITY-BPA): A COMPENDIUM OF PUBLISHED FINDINGS

NTP RR 18

OCTOBER 2021

CLARITY-BPA, Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity

State Interventions

Christine Papagni

Moderated by Margaret Snyder

State Interventions

Christine Papagni

Supervising Environmental Scitentist, Safer Consumer Products Program

California Department of Toxic Substances Control

SAFER CONSUMER PRODUCTS

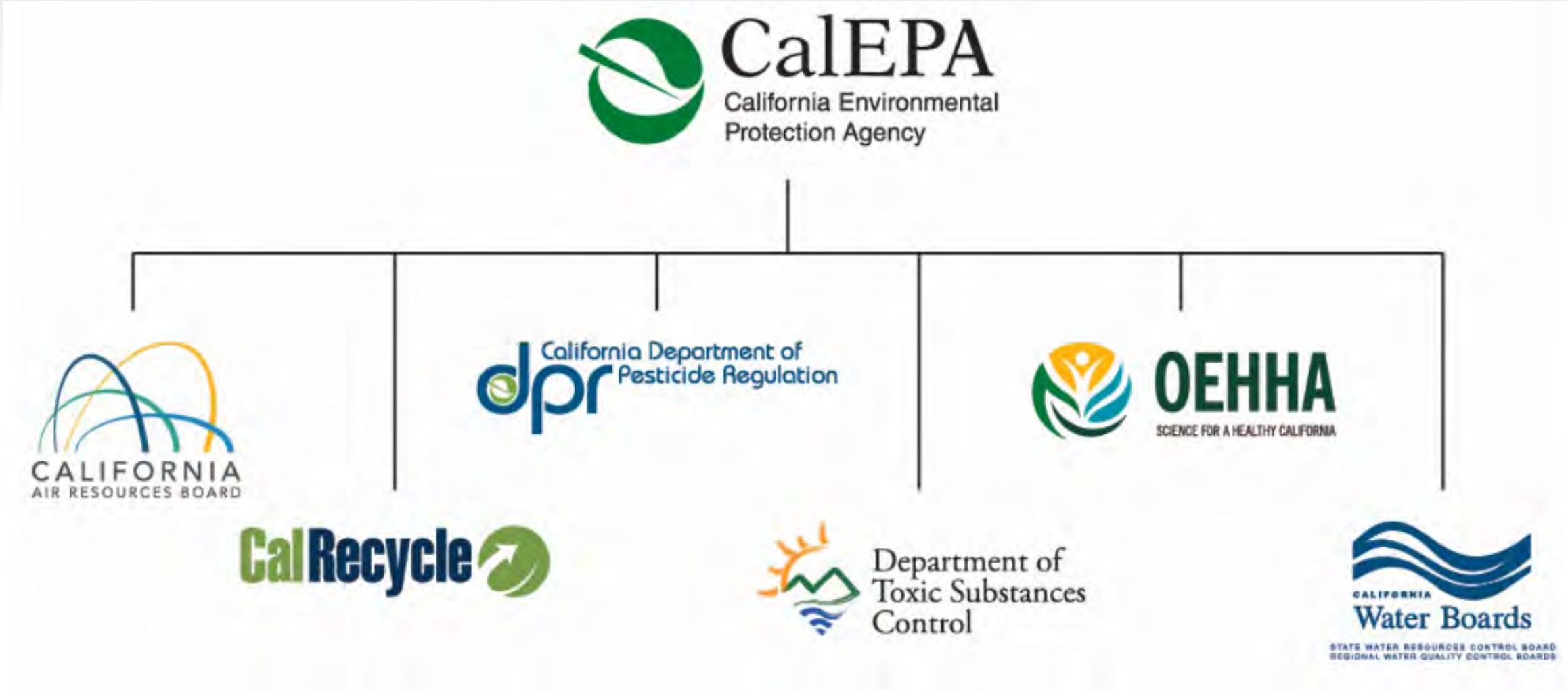
How California is Addressing Endocrine Disruptors in Consumer Products

Christine Papagni
Supervising Scientist, Safer Consumer Products Program

July 19, 2023

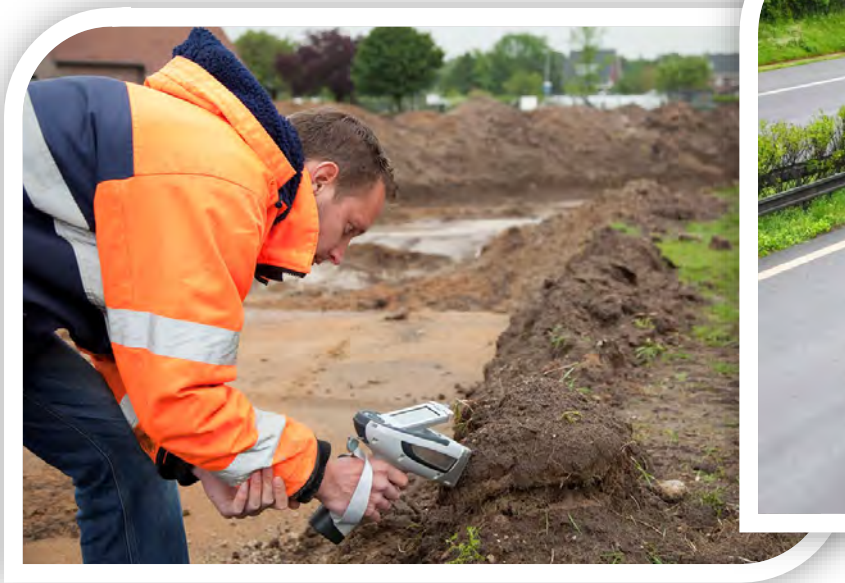
Department of Toxic Substances Control

CalEPA


CalEPA
California Environmental Protection Agency
CALIFORNIA AIR RESOURCES BOARD
California Department of Pesticide Regulation
OEHHA
SCIENCE FOR A HEALTHY CALIFORNIA
CalRecycle
Department of Toxic Substances Control
CALIFORNIA Water Boards
STATE WATER RESOURCES CONTROL BOARD
REGIONAL WATER QUALITY CONTROL BOARDS

DTSC Overview and Safer Consumer Products Program

Past



Site Cleanup

Present

Hazardous Waste Mngt

Future

Safer Consumer Products

Green Chemistry in Policy

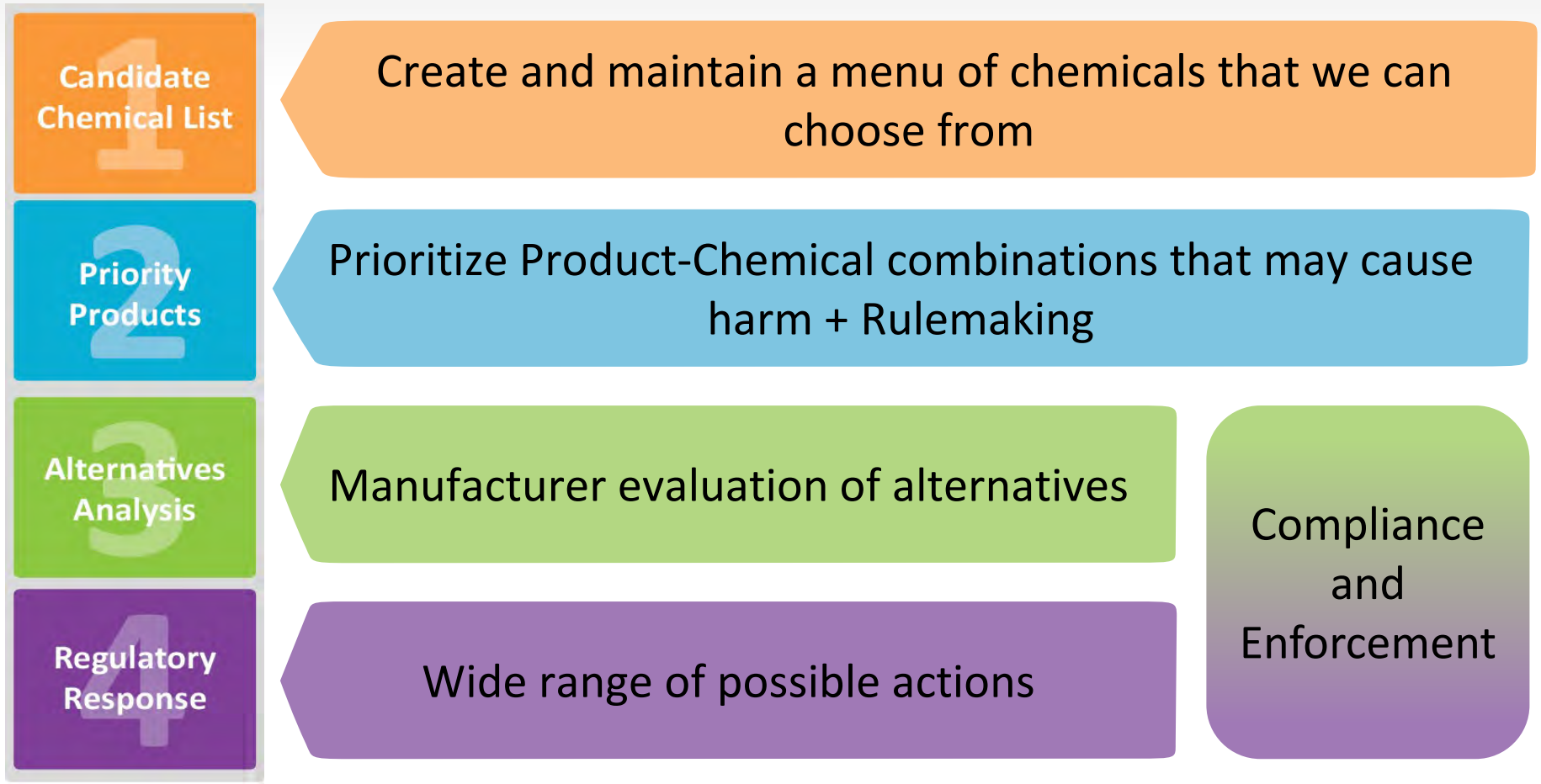
- 2008 California Green Chemistry Law
  - Health and Safety Code section 25252

- Safer Consumer Product Regulations
  - Took effect October 1, 2013
  - CCR Title 22 Chapter 55 Sections 69501 through 69511
- Green Chemistry – Hazard Trait Regulations
  - CCR Title 22 Chapter 55 Sections 69401 through 69407.2

Green Chemistry Law Objectives

- Develop a process to prioritize harmful chemicals in consumer products
- Develop a process to evaluate alternatives to hazardous chemicals
- Avoid regrettable substitutes
- Incentivize innovation and the search for safer alternatives
- Transparent and science-based decision making
- Enforceable

SCP Process


1
Candidate Chemical List
Create and maintain a menu of chemicals that we can choose from
2
Priority Products
Prioritize Product-Chemical combinations that may cause harm + Rulemaking
3
Alternatives Analysis
Manufacturer evaluation of alternatives
4
Regulatory Response
Wide range of possible actions
Compliance and Enforcement

Scope of Products

- Priority Product Work Plan
  - Menu of products
  - Released every 3 years

- Exclusions
  - FIFRA pesticides
  - Prescription drugs
  - Radioactive chemicals
  - Natural toxins

New Work Plan under development!

The 2021-2023 Priority Product Work Plan Categories

Beauty, Personal Care, and Hygiene Products

Building Products and Materials Used in Construction and Renovation

Motor Vehicle Tires

Food Packaging

Cleaning Products

Children's Products

Beauty, Personal Care, and Hygiene Products

- Nail Products
  - PP (toluene, MMA)
  - Info call-in, lab study
    - Dibutyl phthalate (DBP)
    - Diisobutylphthalate (DIBP)
    - Triphenyl phosphate

Beauty, Personal Care, and Hygiene Products (con't)

- Hair Straightening Products
  - Parabens
  - Ortho-phthalates
  - BP-3

- Leave-on products
  - n-butylparaben

Beauty, Personal Care, and Hygiene Products (con't)

- Disposable Menstrual Products (pads and tampons)
  - Ortho-phthalates
  - Parabens
  - Bisphenols

Future Research

- Children's Products
  - Ortho-phthalates screening research
  - Exposure modeling of EDCs
    - Parabens in PCPs
    - Bisphenol A and bisphenol alternatives in toys

Other California Regulations

- California Toxic-Free Cosmetic Act
  - CA HSC §108980
- Cosmetic Fragrance and Flavor Ingredient Right to Know Act of 2020
  - CA HSC §111792.6
- Labeling requirements for professional personal care products
  - CA HSC §110371

Conclusions

- California is trying to address EDCs in multiple ways
- SCP asks manufactures to look for safer alternatives
- Women's and children's health is a policy priority
- Reproductive and developmental effects are a concern
- SCP continues to research Candidate Chemicals in
  - Beauty, personal care, and hygiene
  - Children's products
  - Other Products with EDCs

Contact Information for SCP

- General Questions: Christine.Papagni@dtsc.ca.gov
  SaferConsumerProducts@dtsc.ca.gov

- Join our E-list to get updates: bit.ly/scpupdates

- Learn about career opportunities:
https://dtsc.ca.gov/scp/safer-consumer-products-career-opportunities/

Closing Remarks

Adrienne Smith
Director, Division of Policy and Performance Management
Office on Women's Health
U.S. Department of Health and Human Services

Thank you

The Post-Symposium Knowledge Assessment and Survey will be distributed today!

Thank you for your participation and feedback!

Symposium Website

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